

DESCRIPTION  
BICYCLIC PYRAZOLE DERIVATIVE

TECHNICAL FIELD

The present invention relates to a novel condensed imidazole useful as medicine. More particularly, it relates to a novel condensed imidazole effective as a dipeptidyl peptidase IV (DPP-IV) inhibitor. Furthermore, it relates to a pharmaceutical composition for the treatment of diabetes containing a novel condensed imidazole effective as a dipeptidyl peptidase IV (DPP-IV) inhibitor, as an active ingredient.

BACKGROUND ART

DPP-IV is a serine protease widely present in the body, is one of dipeptidyl aminopeptidases capable of hydrolyzing and releasing a N-terminal peptide and markedly acts on, in particular, peptides containing proline as the second amino acid from the N-terminal. Therefore, DPP-IV is referred to also prolyl end peptidase. DPP-IV is known to accept, as substrates, various biological peptides concerned in the endocrine system, the neuroendocrine system, immunological functions and the like. It is known that many physiologically active peptides such as the pancreatic polypeptide family represented by pancreatic

polypeptides (PP), neuropeptide Y (NPY) and the like;  
the glucagon/VIP family represented by vasoactive  
intestinal polypeptides (VIP), glucagon-like peptide-1  
(GLP-1), glucose-dependent insulintropic polypeptides  
5 (GIP), growth hormone release accelerating factor (GRF)  
and the like; and the chemocaine family are substrates  
for DPP-IV and feel the influences of DPP-IV, such as  
activation/inactivation, metabolism acceleration and  
the like (J. Langer and S. Ansorge, "Cellular  
10 Peptidases in Immune Functions and Disease 2", Advances  
in Experimental Medicine and Biology Vol. 477).

DPP-IV severs two amino acids (His-Ala) from  
the N-terminal of GLP-1. It is known that although the  
severed peptide binds weakly to a GLP-1 receptor, it  
15 has no activating effect on the receptor and acts as an  
antagonist (L.B. Knudsen et al., European Journal of  
Pharmacology, Vol. 318, p429-435, 1996). The  
metabolism of GLP-1 by DPP-IV in blood is known to be  
very rapid, and the concentration of active GLP-1 in  
20 blood is increased by the inhibition of DPP-IV (T.J.  
Kieffer et al., Endocrinology, Vol. 136, p3585-3596,  
1995). GLP-1 is a peptide secreted from intestinal  
tract by the ingestion of sugars and is a main  
accelerating factor for the glucose-responsive  
25 secretion of insulin by pancreas. In addition, GLP-1  
is known to have accelerating effect on insulin  
synthesis in pancreatic  $\beta$  cells and accelerating effect  
on  $\beta$  cell proliferation. Moreover, it is known that

GLP-1 receptors appear also in digestive tracts, liver, muscle, adipose tissue and the like, and it is also known that in these tissues, GLP-1 affects working of digestive tracts, the secretion of acid in stomach, the  
5 synthesis and degradation of glycogen, insulin-dependent glucose uptake, and the like. Accordingly, there is expected the development of a DPP-IV inhibitor effective against type 2 diabetes (non-insulin-dependent diabetes) which brings about effects such as  
10 the acceleration of insulin secretion dependent on blood sugar level, the improvement of pancreas function, the improvement of a high postprandial blood sugar level, the improvement of glucose tolerance abnormality, the improvement of insulin resistance, and  
15 the like, by increasing the concentration of GLP-1 in blood (R.A. Pederson et al., Diabetes Vol. 47, p1253-1258, 1998).

Various DPP-IV inhibitors have been reported. For example, International Publication No. WO02/02560  
20 pamphlet reports that xanthine derivatives having a piperazine ring or the like are effective as DPP-IV inhibitors. International Publication No. WO02/068420 pamphlet and International Publication No. WO03/004496 pamphlet report that xanthine derivatives having a  
25 piperidine ring or the like are effective as DPP-IV inhibitors. International Publication No. WO03/024965 pamphlet reports that xanthine derivatives containing a 2-aminocyclohexylamino group are effective as DPP-IV

inhibitors. International Publication No. WO02/024698 pamphlet reports that xanthine derivatives are effective as phosphodiesterase V inhibitors.

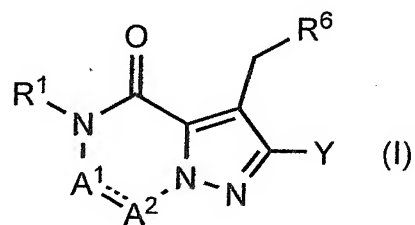
#### DISCLOSURE OF THE INVENTION

5           An object of the present invention is to provide a novel compound having an excellent DPP-IV inhibitory activity.

          The present inventors earnestly investigated in order to achieve the above object, and consequently  
10 found that the following compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug (hereinafter abbreviated as the present inventive compound in some cases if necessary) has an excellent DPP-IV inhibitory effect, whereby the present  
15 invention has been accomplished.

          That is, the present invention relates to the following:

[1]       A compound represented by the formula (I):



wherein R¹ is a hydrogen atom, an optionally substituted  
20 alkyl group, an optionally substituted cycloalkyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

the solid line and dotted line between  $A^1$  and  $A^2$  indicate a double bond ( $A^1=A^2$ ) or a single bond ( $A^1-A^2$ );

$A^1$  is a nitrogen atom or a group represented  
 5 by the formula  $C(R^2)$  and  $A^2$  is a group represented by the formula  $C(R^4)$ , in the case of the solid line and dotted line between  $A^1$  and  $A^2$  being a double bond ( $A^1=A^2$ );

$A^1$  is a group represented by the formula  
 10  $C(R^2)(R^3)$  and  $A^2$  is a group represented by the formula  $C(R^4)(R^5)$ , in the case of the solid line and dotted line between  $A^1$  and  $A^2$  being a single bond ( $A^1-A^2$ );

$R^1$  and  $R^2$  may be taken together with the adjacent nitrogen atom and carbon atom to form an  
 15 optionally substituted 4- to 7-membered ring in the case of the solid line and dotted line between  $A^1$  and  $A^2$  being a double bond ( $A^1=A^2$ ) and  $A^1$  being a group represented by the formula  $C(R^2)$ ;

$R^2$  is a hydrogen atom, a halogen atom, a cyano  
 20 group, a formyl group, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted cycloalkyloxy group, an optionally substituted alkenyl group, an optionally substituted alkynyl group, an optionally substituted  
 25 amino group, an optionally substituted carbamoyl group, a carboxyl group, an optionally substituted alkoxy group, an optionally substituted alkoxycarbonyl group, an optionally substituted cycloalkyloxycarbonyl group,

- a tetrahydrofuranyloxycarbonyl group, an optionally substituted aryl group, an optionally substituted aryloxy group, an optionally substituted aryloxycarbonyl group, an optionally substituted
- 5 aralkyl group, an optionally substituted aralkyloxy group, an optionally substituted aroyl group, an optionally substituted arylthio group, an optionally substituted arylsulfinyl group, an optionally substituted arylsulfonyl group, an optionally
- 10 substituted alkylthio group, an optionally substituted alkylsulfinyl group, an optionally substituted alkylsulfonyl group, an optionally substituted heteroaryl group, an optionally substituted heteroarylalkyl group, an optionally substituted
- 15 heteroarylcarbonyl group, an optionally substituted heteroaryloxy group, an optionally substituted alkylcarbonyl group, an optionally substituted cycloalkylcarbonyl group, or an optionally substituted nitrogen-containing saturated heterocyclic group;
- 20  $R^3$  is a hydrogen atom, a halogen atom, a cyano group, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted carbamoyl group, a carboxyl group, an optionally substituted alkoxy group, an optionally
- 25 substituted alkoxycarbonyl group, an optionally substituted aryl group, an optionally substituted aryloxycarbonyl group, an optionally substituted aralkyl group, an optionally substituted aroyl group,

an optionally substituted aryloxy group, an optionally substituted arylthio group, an optionally substituted arylsulfonyl group, an optionally substituted heteroaryl group, an optionally substituted

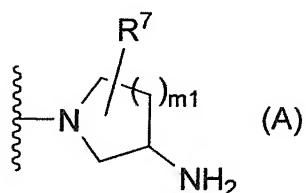
- 5 heteroarylalkyl group, an optionally substituted heteroarylcarbonyl group, an optionally substituted heteroaryloxy group, or an optionally substituted alkylcarbonyl group;

- $R^4$  and  $R^5$  are independently a hydrogen atom, a
- 10 halogen atom, a cyano group, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted carbamoyl group, a carboxyl group, an optionally substituted alkoxy group, an optionally substituted cycloalkyloxy group, an
- 15 optionally substituted alkoxycarbonyl group, an optionally substituted amino group, an optionally substituted aryl group, an optionally substituted aryloxy carbonyl group, an optionally substituted aralkyl group, an optionally substituted aroyl group,
- 20 an optionally substituted aryloxy group, an optionally substituted arylthio group, an optionally substituted arylsulfonyl group, an optionally substituted heteroaryl group, an optionally substituted heteroarylalkyl group, an optionally substituted
- 25 heteroarylcarbonyl group, or an optionally substituted alkylcarbonyl group;

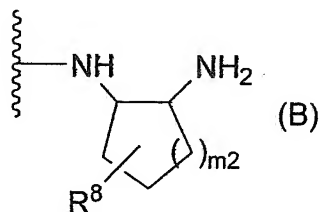
$R^6$  is a hydrogen atom, an optionally substituted alkyl group, an optionally substituted

cycloalkyl group, an optionally substituted aryl group,  
 an optionally substituted vinyl group, an optionally  
 substituted ethynyl group, an optionally substituted  
 nitrogen-containing saturated heterocyclic group, or an  
 5 optionally substituted heteroaryl group; and

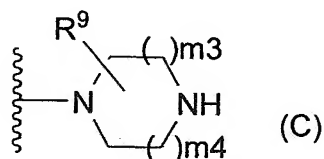
-Y is any of groups represented by the  
 formula (A), formula (B), formula (C) and formula (D)  
 shown below:



wherein  $m_1$  is 0, 1, 2 or 3, and  $R^7$  is absent or one or  
 10 two  $R^7$ 's are present and are independently a halogen  
 atom, a hydroxyl group, an oxo group, an optionally  
 substituted alkoxy group, an optionally substituted  
 alkyl group, an optionally substituted aryl group, an  
 optionally substituted aralkyl group, an optionally  
 15 substituted amino group, a carboxyl group, an  
 optionally substituted alkoxy carbonyl group or an  
 optionally substituted carbamoyl group, or two  $R^7$ 's, when  
 taken together, represent methylene or ethylene and may  
 bind to one or more carbon atoms constituting the ring,  
 20 to form a new ring;

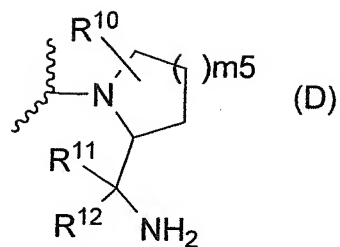


wherein  $m_2$  is 0, 1, 2 or 3, and  $R^8$  is absent or one or two  $R^8$ s are present and are independently a halogen atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted aralkyl group, an optionally substituted amino group, a carboxyl group, an optionally substituted alkoxy carbonyl group or an optionally substituted carbamoyl group, or two  $R^8$ s, when taken together, represent methylene or ethylene and may bind to one or more carbon atoms constituting the ring, to form a new ring;



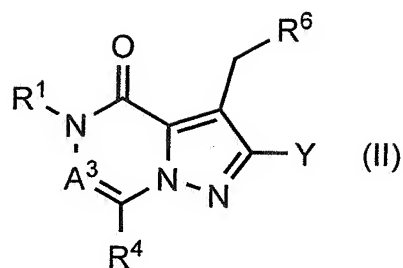
wherein  $m_3$  and  $m_4$  are independently 0 or 1, and  $R^9$  is absent or one or two  $R^9$ s are present and are independently a halogen atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted aralkyl group, an optionally substituted amino group, a carboxyl group, an optionally substituted alkoxy carbonyl group or an optionally substituted carbamoyl group, or two  $R^9$ s, when taken together, represent methylene or ethylene and may bind to one or more carbon atoms constituting the ring, to form a new

ring; and



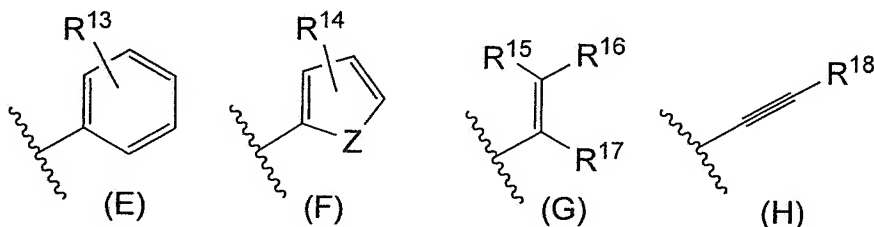
wherein  $m_5$  is 1, 2 or 3,  $R^{10}$  is absent or one or two  $R^{10}$ s are present and are independently a halogen atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted aralkyl group, an optionally substituted amino group, a carboxyl group, an optionally substituted alkoxycarbonyl group or an optionally substituted carbamoyl group, or two  $R^{10}$ s, when taken together, represent methylene or ethylene and may bind to one or more carbon atoms constituting the ring, to form a new ring, and  $R^{11}$  and  $R^{12}$  are independently a hydrogen atom, methyl, ethyl, propyl or isopropyl, or  $R^{11}$  and  $R^{12}$ , when taken together with the adjacent carbon atom, represent cyclopropyl, cyclobutyl or cyclopentyl, a prodrug of said compound, or a pharmaceutically acceptable salt of said compound or prodrug.

[2] A compound according to [1], which is represented by the formula (II):



wherein  $A^3$  is a nitrogen atom or a group represented by the formula  $C(R^2)$ , and  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^6$  and  $Y$  are as defined in the item [1], a prodrug thereof or a pharmaceutically acceptable salt of the compound or  
 5 prodrug.

[3] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to [1] or [2], wherein  $R^6$  is the following formula (E), formula (F), formula (G) or formula (H):



10 wherein  $Z$  is an oxygen atom, the formula  $S(O)_p$  or  $N(R^{19})$ ;

$R^{13}$  is absent or one or two  $R^{13}$ s are present and are independently a halogen atom, a hydroxyl group, a formyl group, a carboxyl group, a cyano group, an  
 15 alkylthio group, an alkylsulfinyl group, an alkylsulfonyl group, an alkyl group, a haloalkyl group,

a cycloalkyl group, an alkoxy group, a haloalkoxy group, an optionally substituted amino group, an optionally substituted carbamoyl group, an alkoxycarbonyl group, an optionally substituted alkylcarbonyl group, a cycloalkylcarbonyl group, an optionally substituted phenyl group, an optionally substituted heteroaryl group or a nitrogen-containing saturated heterocyclic group, or two  $R^{13}$ s, when taken together, represent a  $C_{1-3}$  alkylenedioxy group;

10  $R^{14}$  is absent or one or two  $R^{14}$ s are present and are independently a halogen atom, a cyano group, an alkyl group, a haloalkyl group, a cycloalkyl group, an alkoxy group or a haloalkoxy group;

$R^{15}$  is methyl, ethyl, a chlorine atom or a bromine atom;

$R^{16}$  is a hydrogen atom, methyl, ethyl, a chlorine atom or a bromine atom;

$R^{17}$  is a hydrogen atom, methyl or ethyl;

$R^{18}$  is a hydrogen atom, methyl, ethyl, cyclopropyl or cyclobutyl;

$p$  is 0, 1 or 2; and

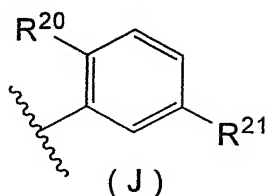
$R^{19}$  is a hydrogen atom or an alkyl group.

[4] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to [3], wherein  $R^6$  is the formula (E) or the formula (H).

[5] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug

according to [4], wherein  $R^6$  is the formula (E) and one or two  $R^{13}$  are present and are independently a halogen atom, a cyano group, an alkylthio group, an alkylsulfonyl group, a  $C_{1-3}$  alkylenedioxy group, an alkyl group, a haloalkyl group, a cycloalkyl group, an alkoxy group or a haloalkoxy group.

[6] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to either of [1] and [2], wherein  $R^6$  is the following formula (J):



wherein  $R^{20}$  is a halogen atom, a cyano group, an alkylthio group, an alkylsulfonyl group, an alkyl group, a haloalkyl group, a cycloalkyl group, an alkoxy group or a haloalkoxy group, and  $R^{21}$  is a hydrogen atom or a fluorine atom.

[7] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [6], wherein Y is the formula (A) or (B).

[8] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [6], wherein Y is the formula (A).

[9] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [8], wherein  $R^2$  is a hydrogen atom, a cyano group, an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted alkenyl group, an optionally substituted carbamoyl group, a carboxyl group, an optionally substituted alkoxycarbonyl group, an optionally substituted cycloalkyloxycarbonyl group, a tetrahydrofuranyloxycarbonyl group, an optionally substituted aryl group, an optionally substituted aryloxycarbonyl group, an optionally substituted aralkyl group, an optionally substituted aroyl group, an optionally substituted heteroaryl group, an optionally substituted heteroarylalkyl group, an optionally substituted heteroarylcarbonyl group or an optionally substituted alkylcarbonyl group.

[10] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [8], wherein  $R^2$  is a hydrogen atom, a cyano group, an optionally substituted alkyl group, an optionally substituted carbamoyl group, a carboxyl group, an optionally substituted alkoxycarbonyl group, an optionally substituted cycloalkyloxycarbonyl group, a tetrahydrofuranyloxycarbonyl group, an optionally substituted aryl group, an optionally substituted aryloxycarbonyl group, an optionally substituted aralkyl group, an

optionally substituted aroyl group, an optionally substituted heteroaryl group or an optionally substituted alkylcarbonyl group.

[11] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [10], wherein  $R^4$  is a hydrogen atom, an optionally substituted alkyl group, a cyano group, an optionally substituted carbamoyl group, a carboxyl group, an optionally substituted alkoxy group, an optionally substituted cycloalkyloxy group, an optionally substituted alkoxycarbonyl group, an optionally substituted aryl group, an optionally substituted aryloxy carbonyl group, an optionally substituted aralkyl group, an optionally substituted aroyl group, an optionally substituted heteroaryl group, an optionally substituted heteroarylalkyl group, an optionally substituted heteroarylcarbonyl group or an optionally substituted alkylcarbonyl group.

[12] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [10], wherein  $R^4$  is a hydrogen atom or an optionally substituted alkyl group.

[13] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [10], wherein  $R^4$  is the formula:  $-C(R^{22})(R^{23})-A^4-R^{24}$  in which  $R^{22}$  and  $R^{23}$  are independently a hydrogen atom, methyl, ethyl, propyl, isopropyl, methoxy or ethoxy, or  $R^{22}$  and  $R^{23}$ , when taken

together with the adjacent carbon atom, represent cyclopropyl, cyclobutyl or cyclopentyl; A<sup>4</sup> is a single bond, methylene or ethylene; and R<sup>24</sup> is a hydrogen atom, a cyano group, an alkyl group, a haloalkyl group, a cycloalkyl group, a tetrahydrofuranyl group, an optionally substituted carbamoyl group, a carboxyl group, an optionally substituted alkoxy group, an optionally substituted aryloxy group, an optionally substituted alkoxycarbonyl group, an optionally substituted aryl group, an optionally substituted aryloxy carbonyl group, an optionally substituted aroyl group, an optionally substituted heteroarylcarbonyl group or an optionally substituted alkylcarbonyl group.

[14] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [13], wherein R<sup>1</sup> is a hydrogen atom, an optionally substituted alkyl group of 1 to 3 carbon atoms, or an optionally substituted aryl group, and the substituent(s) of the optionally substituted alkyl group is selected from fluorine atom, optionally substituted aroyl groups, carboxyl group, optionally substituted alkoxycarbonyl groups, optionally substituted aryl groups and optionally substituted aryloxy groups.

[15] A compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [13], wherein R<sup>1</sup> is a hydrogen atom, methyl or a group represented by the

formula: -Ra-Rb-Rc in which

Ra is an alkylene chain;

Rb is a single bond or a carbonyl group; and

Rc is an optionally substituted alkyl group,

5 an optionally substituted alkoxy group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted heteroaryloxy group or an optionally substituted aryloxy group.

10 [16] A pharmaceutical composition comprising a compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [15] as an active ingredient.

[17] A dipeptidyl peptidase IV inhibitor  
15 comprising a compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [15] as an active ingredient.

[18] A pharmaceutical composition for the  
20 treatment of diabetes comprising a compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [15] as an active ingredient.

[19] Use of a compound, a prodrug thereof or a  
25 pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [15] in the manufacture of a dipeptidyl peptidase IV inhibitor.

[20] Use of a compound, a prodrug thereof or a

pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [15] in the manufacture of a pharmaceutical composition for the treatment of diabetes.

5 [21] A method for treating diabetes comprising administering an effective amount of a compound, a prodrug thereof or a pharmaceutically acceptable salt of the compound or prodrug according to any one of [1] to [15] to a patient who needs treatment.

10 The present inventive compound has an excellent DPP-IV inhibitory activity and is useful as a therapeutic agent for diabetes.

The present invention is explained below in further detail.

15 In the present specification, the number of substituents of each group defined by the term "optionally substituted" or "substituted" is not particularly limited so long as the substitution is possible, and it is 1 or more. Unless otherwise  
20 specified, the explanation of each group applies also to the case where the group is a portion or the substituent of another group.

The "halogen atom" includes, for example, fluorine atom, chlorine atom, bromine atom and iodine  
25 atom.

The "alkyl group" includes, for example, linear or branched alkyl groups of 1 to 6 carbon atoms. Specific examples thereof are methyl, ethyl, propyl,

isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl and 2-ethylbutyl. Preferable examples  
5 thereof are linear or branched alkyl groups of 1 to 4 carbon atoms. Specific examples of such groups are methyl, ethyl, propyl, isopropyl, butyl and tert-butyl.

The "alkenyl group" includes, for example, alkenyl groups of 2 to 6 carbon atoms. Specific  
10 examples thereof are vinyl, propenyl, methylpropenyl, butenyl and methylbutenyl.

The "alkynyl group" includes, for example, alkynyl groups of 2 to 6 carbon atoms. Specific examples thereof are ethynyl, 1-propynyl, 2-propynyl,  
15 butynyl, pentynyl and hexynyl.

The "cycloalkyl group" includes, for example, cycloalkyl groups of 3 to 10 carbon atoms. Specific examples thereof are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl and  
20 norbornyl. Preferable examples thereof are cycloalkyl groups of 3 to 6 carbon atoms. Specific examples of such groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The "aryl group" includes, for example, aryl  
25 groups of 6 to 10 carbon atoms. Specific examples thereof are phenyl, 1-naphthyl and 2-naphthyl.

The "aralkyl group" includes, for example, groups formed by bonding of an aryl group to an

alkylene chain. Specific examples thereof are benzyl, 2-phenylethyl and 1-naphthylmethyl.

The "alkylene chain" includes, for example, alkylene chains of 1 to 3 carbon atoms. Specific  
5 examples thereof are methylene, ethylene and trimethylene.

The "heteroaryl group" includes, for example, 5- to 10-membered monocyclic or polycyclic groups containing one or more (for example, 1 to 4)  
10 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom. Specific examples thereof are pyrrolyl, thienyl, benzothienyl, benzofuranyl, benzoxazolyl, benzothiazolyl, furyl, oxazolyl, thiazolyl, isoxazolyl, imidazolyl, pyrazolyl, pyridyl,  
15 pyrazyl, pyrimidyl, pyridazyl, quinolyl, isoquinolyl, triazolyl, triazinyl, tetrazolyl, indolyl, imidazo[1,2-a]pyridyl, dibenzofuranyl, benzimidazolyl, quinoxalyl, cinnolyl, quinazolyl, indazolyl, naphthyridyl, quinolinolyl and isoquinolinolyl. Preferable examples  
20 thereof are 5- or 6-membered groups containing a heteroatom selected from nitrogen atom, sulfur atom and oxygen atom. Specific examples of such groups are pyridyl, thienyl and furyl.

The heteroaryl portion of the  
25 "heteroarylalkyl group" includes the groups exemplified above as the heteroaryl group.

The "alkylcarbonyl group" includes, for example, alkylcarbonyl groups of 2 to 4 carbon atoms.

Specific examples thereof are acetyl, propionyl and butyryl.

The "cycloalkylcarbonyl group" includes, for example, cycloalkylcarbonyl groups of 4 to 11 carbon  
5 atoms. Specific examples thereof are cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, adamantylcarbonyl and norbornylcarbonyl. Preferable examples thereof are cycloalkylcarbonyl groups of 4 to  
10 7 carbon atoms. Specific examples of such groups are cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl and cyclohexylcarbonyl.

The "aroyl group" includes, for example, aroyl groups of 7 to 11 carbon atoms. Specific  
15 examples thereof are benzoyl, 1-naphthoyl and 2-naphthoyl.

The heteroaryl portion of the "heteroarylcarbonyl group" includes the groups exemplified above as the heteroaryl group.

20 The "alkoxycarbonyl group" includes, for example, alkoxycarbonyl groups of 2 to 5 carbon atoms. Specific examples thereof are methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, 2-propoxycarbonyl and tert-butoxycarbonyl.

25 The "aryloxycarbonyl group" includes, for example, aryloxycarbonyl groups of 7 to 11 carbon atoms. Specific examples thereof are phenyloxycarbonyl, 2-naphthyloxy-carbonyl and 1-

naphthyloxycarbonyl.

The "alkoxy group" includes, for example, alkoxy groups of 1 to 4 carbon atoms. Specific examples thereof are methoxy, ethoxy, propoxy,  
5 isopropoxy, butoxy, isobutoxy, sec-butoxy and tert-butoxy.

The "cycloalkyloxy group" includes, for example, cycloalkyloxy groups of 3 to 10 carbon atoms. Specific examples thereof are cyclopropyloxy,  
10 cyclobutoxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, adamantyloxy and norbornyloxy. Preferable examples thereof are cycloalkyloxy groups of 3 to 6 carbon atoms. Specific examples of such groups are cyclopropyloxy, cyclobutoxy, cyclopentyloxy and  
15 cyclohexyloxy.

The "aryloxy group" includes, for example, aryloxy groups of 6 to 10 carbon atoms. Specific examples thereof are phenoxy, 1-naphthyloxy and 2-naphthyloxy.

20 The aralkyl portion of the "aralkyloxy group" includes the groups exemplified above as the aralkyl group. Specific examples thereof are benzyloxy and 2-phenylethyloxy.

The heteroaryl portion of the "heteroaryloxy group" includes the groups exemplified above as the  
25 heteroaryl group.

The "alkylthio group" includes, for example, alkylthio groups of 1 to 6 carbon atoms. Specific

examples thereof are methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, pentylthio and hexylthio. Preferable examples thereof are alkylthio groups of 1 to 4 carbon  
5 atoms. Specific examples of such groups are methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio and tert-butylthio.

The "alkylsulfinyl group" includes, for example, alkylsulfinyl groups of 1 to 6 carbon atoms.  
10 Specific examples thereof are methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, pentylsulfinyl and hexylsulfinyl. Preferable examples thereof are alkylsulfinyl groups of 1 to 4 carbon atoms. Specific examples of such groups  
15 are methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl and butylsulfinyl.

The "alkylsulfonyl group" includes, for example, alkylsulfonyl groups of 1 to 6 carbon atoms. Specific examples thereof are methylsulfonyl,  
20 ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, pentylsulfonyl and hexylsulfonyl. Preferable examples thereof are alkylsulfonyl groups of 1 to 4 carbon atoms. Specific examples of such groups are methylsulfonyl, ethylsulfonyl, propylsulfonyl,  
25 isopropylsulfonyl and butylsulfonyl.

The "arylthio group" includes, for example, arylthio groups of 6 to 10 carbon atoms. Specific examples thereof are phenylthio, 1-naphthylthio and 2-

naphthylthio.

The "arylsulfinyl group" includes, for example, arylsulfinyl groups of 6 to 10 carbon atoms. Specific examples thereof are phenylsulfinyl, 1-  
5 naphthylsulfinyl and 2-naphthylsulfinyl.

The "arylsulfonyl group" includes, for example, arylsulfonyl groups of 6 to 10 carbon atoms. Specific examples thereof are phenylsulfonyl, tosyl, 1-naphthylsulfonyl and 2-naphthylsulfonyl.

10 The "nitrogen-containing saturated heterocyclic group" includes, for example, 5- or 6-membered saturated heterocyclic rings which have one or two nitrogen atoms and may further have an oxygen atom or a sulfur atom. Specific examples thereof are  
15 pyrrolidinyl, imidazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, dioxothiomorpholinyl, hexamethyleniminyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, oxoimidazolidinyl, dioxoimidazolidinyl, oxooxazolidinyl, dioxooxazolidinyl, dioxothiazolidinyl,  
20 tetrahydrofuranyl and tetrahydropyridinyl.

The substituent(s) of the "optionally substituted alkyl group" includes, for example, (1) halogen atoms, (2) hydroxyl group, (3) cyano group, (4) carboxyl group, (5) optionally substituted cycloalkyl  
25 groups, (6) optionally substituted aryl groups, (7) optionally substituted heteroaryl groups, (8) optionally substituted aroyl groups, (9) optionally substituted heteroarylcarbonyl groups, (10) optionally

substituted arylaminocarbonyl groups, (11) optionally substituted heteroarylaminocarbonyl groups, (12) optionally substituted aryloxy groups, (13) optionally substituted arylsulfonyl groups, (14) optionally substituted aralkylsulfonyl groups, (15) optionally substituted alkoxy groups, (16) optionally substituted cycloalkyloxy groups, (17) optionally substituted alkoxy carbonyl groups, (18) optionally substituted aryloxy carbonyl groups, (19) optionally substituted amino groups, (20) optionally substituted carbamoyl groups, (21) alkylsulfonyl groups, (22) optionally substituted vinyl groups, (23) optionally substituted ethynyl groups, (24) optionally substituted alkyl carbonyl groups, (25) cycloalkyloxycarbonyl groups, (26) optionally substituted quinolonyl groups, (27) optionally substituted isoquinolonyl groups, (28) tetrahydrofuranyloxycarbonyl group, and (29) tetrahydrofuranlyl group.

Here, the above items (1) to (29) are explained below.

The substituents of the "optionally substituted cycloalkyl groups" of the above item (5) include, for example, alkyl groups, aralkyl groups, alkoxy groups and fluorine atom.

The substituents of the "optionally substituted aryl groups" of the above item (6) include those hereinafter exemplified as the substituents of the "optionally substituted aryl groups".

The substituents of the "optionally substituted heteroaryl groups" of the above item (7) include, for example,

- (a) hydroxyl group,
- 5 (b) halogen atoms,
- (c) alkyl groups,
- (d) alkyl groups substituted by a halogen atom(s) or an alkoxy group (for example, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 10 2,2,2-trifluoroethyl, perfluoroethyl, 2-fluoro-1-(fluoromethyl)ethyl, 1-(difluoromethyl)-2,2-difluoroethyl, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy and ethoxypropoxy),
- 15 (e) alkoxy groups,
- (f) alkoxy groups substituted by a halogen atom(s) or an alkoxy group (for example, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy, 2-fluoro-1- 20 (fluoromethyl)ethoxy, 1-(difluoromethyl)-2,2-difluoroethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy and ethoxypropoxy),
- (g) cyano group,
- 25 (h) carboxyl group,
- (i) alkoxycarbonyl groups,
- (j) carbamoyl groups which may be substituted by an alkyl group(s) (for example, carbamoyl,

methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl and diethylcarbamoyl),

(k) aryl groups,

and (l) amino group.

5           The substituents of the "optionally substituted aroyl groups" of the above item (8) include those exemplified as the substituents of the "optionally substituted aryl groups" of the above item (6).

10           The substituents of the "optionally substituted heteroarylcarbonyl groups" of the above item (9) include those exemplified as the substituents of the "optionally substituted heteroaryl groups" of the above item (7).

15           The substituents of the "optionally substituted arylaminocarbonyl groups" of the above item (10) include those exemplified as the substituents of the "optionally substituted aryl groups" of the above item (6).

20           The substituents of the "optionally substituted heteroarylaminocarbonyl groups" of the above item (11) include those exemplified as the substituents of the "optionally substituted heteroaryl groups" of the above item (7).

25           The substituents of the "optionally substituted aryloxy groups" of the above item (12) and the "optionally substituted arylsulfonyl groups" of the above item (13) include those exemplified as the

substituents of the "optionally substituted aryl groups" of the above item (6).

The aralkyl portion of each of the "optionally substituted aralkylsulfonyl groups" of the  
5 above item (14) includes the groups exemplified above as the aralkyl group.

The substituents of the "optionally substituted aralkylsulfonyl groups" include those exemplified as the substituents of the "optionally  
10 substituted aryl groups" of the above item (6).

The substituents of the "optionally substituted alkoxy groups" of the above item (15) include, for example,

- (a) hydroxyl group,
- 15 (b) carboxyl group,
- (c) alkyl groups,
- (d) alkoxy groups,
- (e) alkylcarbonyloxy groups (for example, methylcarbonyloxy, ethylcarbonyloxy, propylcarbonyloxy,  
20 isopropylcarbonyloxy, butylcarbonyloxy and tert-butylcarbonyloxy),
- (f) alkoxycarbonyl groups,
- (g) amino groups substituted by an alkyl group(s),
- (h) carbamoyl groups substituted by an alkyl group(s),
- 25 (i) sulfamoyl groups substituted by an alkyl group(s),
- (j) ureido groups substituted by an alkyl group(s),
- (k) alkoxycarbonyloxy groups (for example, methoxycarbonyloxy, ethoxycarbonyloxy, 2-propoxycarbonyloxy,

- and tert-butoxycarbonyloxy),
- (l) cycloalkyloxycarbonyloxy groups (for example, cyclopentyloxycarbonyloxy, cyclohexyloxycarbonyloxy and cycloheptyloxycarbonyloxy),
- 5 (m) phenyl groups which may be substituted by a halogen atom or an alkoxy group (for example, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-isopropoxyphenyl and 3-isopropoxyphenyl),
- (n) 5-methyl-2-oxo-1,3-dioxolen-4-yl,
- (o) 5-oxo-2-tetrahydrofuranyl,
- (p) 1,3-dihydro-3-oxo-1-isobenzofuranyl,
- 15 (q) tetrahydrofuranyl,
- (r) nitrogen-containing saturated heterocyclic groups,
- (s) alkoxy groups substituted by a halogen atom(s) or an alkoxy group (for example, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy, 2-fluoro-1-(fluoromethyl)ethoxy, 1-(difluoromethyl)-2,2-difluoroethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy and ethoxypropoxy),
- 20 (t) cycloalkyl groups,
- (u) cycloalkyl groups substituted by a halogen atom(s) or an alkoxy group (for example, 2-fluorocyclopropyl, 2-methoxycyclopropyl, 2-fluorocyclobutyl, 3-

fluorocyclobutyl and 3-methoxycyclobutyl),  
and (v) halogen atoms.

The substituents of the "optionally substituted cycloalkyloxy groups" of the above item  
5 (16) and the "optionally substituted alkoxy carbonyl groups" of the above item (17) include those exemplified as the substituents of the "optionally substituted alkoxy groups" of the above item (15).

The substituents of the "optionally substituted aryloxy carbonyl groups" of the above item  
10 (18) include those exemplified as the substituents of the "optionally substituted aryl groups" of the above item (6).

The substituents of the "optionally substituted amino groups" of the above item (19)  
15 include, for example,  
(a) alkyl groups,  
(b) alkyl carbonyl groups,  
(c) aryl groups,  
20 (d) alkyl sulfonyl groups,  
(e) aryl sulfonyl groups,  
(f) optionally substituted aryl groups (whose substituent(s) includes, for example, halogen atoms, alkyl groups and alkoxy groups),  
25 (g) alkoxy carbonyl methyl (the carbon atom of the methyl portion may be substituted by one or two alkyl groups, and the two alkyl groups on the carbon atom of the methyl portion may bind to each other to form

cyclopropyl, cyclobutyl or cyclopentyl together with the carbon atom of the methyl portion), and (h) aralkyl groups.

As the optionally substituted amino groups,  
5 (i) imides are also exemplified.

The substituents of the "optionally substituted carbamoyl groups" of the above item (20) include, for example, alkyl groups and cycloalkyl groups. The two substituents of the carbamoyl group  
10 may bind to each other to form an aliphatic heterocyclic ring which may contain carbon, nitrogen or oxygen, such as pyrrolidine (which may be substituted by a hydroxyl group), piperidine, morpholine, thiomorpholine, thiomorpholine oxide, thiomorpholine  
15 dioxide, piperazine (whose nitrogen atom may be substituted by methyl or ethyl), or the like.

Specific examples of the "optionally substituted carbamoyl groups" are carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl,  
20 diethylcarbamoyl, ethylmethylcarbamoyl, methylpropylcarbamoyl, cyclopropylcarbamoyl, cyclopropylmethylcarbamoyl, pyrrolidinocarbonyl, piperidinocarbonyl and morpholinocarbonyl.

The substituents of the "optionally substituted vinyl groups" of the above item (22)  
25 include, for example, halogen atoms and alkyl groups.

Specific examples of the substituted vinyl groups are 1-propylene, 2-methyl-1-propylene and 2-

chloro-1-propylene.

The substituents of the "optionally substituted ethynyl groups" of the above item (23) include, for example, alkyl groups and cycloalkyl groups.

Specific examples of the substituted ethynyl groups are ethylidyne, propylidyne and 2-cyclopropyl-1-ethylidyne.

The substituents of the "optionally substituted alkylcarbonyl groups" of the above item (24) include, for example,

- (a) halogen atoms,
- (b) alkoxy groups,
- (c) cycloalkyl groups,
- (d) alkoxy carbonyl groups,
- and (e) optionally substituted aryl groups (whose substituent(s) includes, for example, halogen atoms, alkyl groups, alkoxy groups and alkoxy carbonyl groups).

The substituents of the "optionally substituted quinolonyl groups" of the above item (26) and the "optionally substituted isoquinolonyl groups" of the above item (27) include, for example, alkyl groups.

The substituent(s) of each of the "optionally substituted alkylthio group", "optionally substituted alkylsulfinyl group" and "optionally substituted alkylsulfonyl group" includes those exemplified as the substituents of the above-mentioned "optionally

substituted alkyl group".

The substituent(s) of each of the "optionally substituted alkenyl group" and the "optionally substituted alkynyl group" includes

- 5 (1) hydroxyl group,
  - (2) halogen atoms,
  - (3) alkyl groups,
  - (4) alkyl groups substituted by a halogen atom(s) or an alkoxy group (for example, fluoromethyl,
  - 10 difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2-fluoro-1-(fluoromethyl)ethyl, 1-(difluoromethyl)-2,2-difluoroethyl, methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl, methoxypropyl and
  - 15 ethoxypropyl),
  - (5) alkoxy groups,
  - (6) alkoxy groups substituted by a halogen atom(s) or an alkoxy group (for example, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy,
  - 20 2,2,2-trifluoroethoxy, perfluoroethoxy, 2-fluoro-1-(fluoromethyl)ethoxy, 1-(difluoromethyl)-2,2-difluoroethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy and ethoxypropoxy),
  - 25 (7) phenyl groups or aroyl groups, which may be substituted by the following (aa), (bb) or (cc):
- (aa) an alkoxy group which may be substituted by a halogen atom(s) or an alkoxy group

(for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy, 2-fluoro-1-(fluoromethyl)ethoxy, 1-(difluoromethyl)-2,2-difluoroethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy or ethoxypropoxy),

(bb) an alkyl group which may be substituted by a halogen atom(s) (for example, methyl, ethyl, propyl, isopropyl, butyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2-fluoro-1-(fluoromethyl)ethyl or 1-(difluoromethyl)-2,2-difluoroethyl),

(cc) a halogen atom(s),

- (8) cyano group,
- (9) carboxyl group,
- (10) alkoxycarbonyl groups,
- (11) carbamoyl groups which may be substituted by an alkyl group(s) (for example, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl and diethylcarbamoyl),
- (12) alkylsulfonyl groups,
- and (13) phenyloxy.

The substituent(s) of the "optionally substituted vinyl group" includes those exemplified as the substituents of (22) the "optionally substituted

vinyl groups" as the substituent(s) of the above-mentioned "optionally substituted alkyl group".

The substituent(s) of the "optionally substituted ethynyl group" includes those exemplified  
5 as the substituents of (23) the "optionally substituted ethynyl groups" as the substituent(s) of the above-mentioned "optionally substituted alkyl group".

The substituent(s) of the "optionally substituted cycloalkyl group" includes those  
10 exemplified as the substituents of (5) the "optionally substituted cycloalkyl groups" as the substituent(s) of the above-mentioned "optionally substituted alkyl group".

The substituent(s) of the "optionally substituted aryl group" includes, for example,  
15 (1) hydroxyl group,  
(2) halogen atoms,  
(3) alkyl groups,  
(4) alkyl groups substituted by a halogen atom(s), an  
20 alkoxy group or a cycloalkyl group (for example, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2-fluoro-1-(fluoromethyl)ethyl, 1-(difluoromethyl)-2,2-difluoroethyl, methoxymethyl, ethoxymethyl,  
25 methoxyethyl, ethoxyethyl, methoxypropyl and ethoxypropyl),  
(5) phenyl groups which may be substituted by the following (aa), (bb) or (cc):

(aa) an alkoxy group which may be substituted by a halogen atom(s) or an alkoxy group (for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, tert.-butoxy, 5 fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy, 2-fluoro-1-(fluoromethyl)ethoxy, 1-(difluoromethyl)-2,2-difluoroethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy or 10 ethoxypropoxy),

(bb) an alkyl group which may be substituted by a halogen atom(s) (for example, methyl, ethyl, propyl, isopropyl, butyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 2,2,2- 15 trifluoroethyl, perfluoroethyl, 2-fluoro-1-(fluoromethyl)ethyl or 1-(difluoromethyl)-2,2-difluoroethyl),

(cc) a halogen atom(s),

- (6) cyano group,
- 20 (7) carboxyl group,
- (8) alkoxycarbonyl groups which may be substituted by a halogen atom(s) (for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, fluoromethoxycarbonyl, 25 difluoromethoxycarbonyl, 2,2-difluoroethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, methoxycarbonyl and ethoxycarbonyl),
- (9) carbamoyl groups which may be substituted by an

- alkyl group(s) (for example, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl and diethylcarbamoyl),
- (10) alkylsulfonyl groups,
- 5 (11) C<sub>1-3</sub> alkylenedioxy groups,
- (12) formyl group,
- (13) optionally substituted phenyloxy groups (whose substituent(s) includes, for example, halogen atoms, alkyl groups and alkoxy groups),
- 10 (14) nitrogen-containing saturated heterocyclic groups (for example, pyrrolidinyl, piperidinyl, morpholinyl and piperazinyl (whose nitrogen atoms may be substituted, for example, by methyl, ethyl or propyl)),
- (15) cycloalkyloxy groups which may be substituted by
- 15 a hydroxyl group, an oxo group, a carboxyl group, a carboxymethyl group, an alkoxycarbonyl group, an alkoxycarbonylalkyl group (e.g. methoxycarbonylmethyl, ethoxycarbonylmethyl or isopropoxycarbonylmethyl), an alkyl group, a fluoroalkyl group (e.g. fluoromethyl,
- 20 difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or perfluoroethyl), an alkoxyalkyl group (e.g. methoxymethyl, ethoxymethyl or isopropoxymethyl), a cycloalkyloxyalkyl group (e.g. cyclopropyloxymethyl, cyclopropyloxyethyl or
- 25 cyclobutoxy), an alkoxy group, a cycloalkyloxy group or a halogen atom(s) (for example, 3-carboxycyclobutoxy, 3-methoxycarbonylcyclobutoxy, 3-ethoxycarbonylbutoxy, 2-methylcyclopropyloxy, 2-fluorocyclopropyloxy, 3-

- methoxycyclobutoxy, 3-fluorocyclobutoxy, 3,3-difluorocyclobutoxy and 3-(2-fluoroethyl)cyclobutoxy),
- (16) alkoxy groups which may be substituted by a hydroxyl group, an oxo group, a carboxyl group, an
- 5 alkoxy carbonyl group, a cycloalkyl group, an alkoxy group, a cycloalkyloxy group, an optionally substituted oxygen-containing heterocyclic group (e.g. a 5- or 6-membered saturated heterocyclic group having an oxygen atom(s), specific examples of which are tetra-
- 10 hydrofuranyl and tetrahydropyranyl; its substituent(s) includes, for example, halogen atoms, oxo group and alkoxy groups), or a halogen atom(s) (for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, 2-hydroxyethoxy,
- 15 carboxymethoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, tert-butoxycarbonylmethoxy, cyclopropylmethoxy, cyclobutylmethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, isopropoxymethoxy, cyclopropyloxymethoxy, cyclobutoxymethoxy,
- 20 fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy, 2-fluoro-1-(fluoromethyl)ethoxy and 1-(difluoromethyl)-2,2-difluoroethoxy),
- (17) difluoromethylenedioxy,
- 25 (18) alkenyl groups which may be substituted by a halogen atom(s) (for example, vinyl, propenyl, methylpropenyl, butenyl and methylbutenyl),
- (19) amino groups which may be substituted by an alkyl

group(s) (for example, amino, methylamino, ethylamino, propylamino, dimethylamino, methylethylamino and diethylamino),

(20) optionally substituted alkylcarbonyl groups

5 (whose substituent(s) includes, for example, halogen atoms, alkoxy groups and cycloalkyl groups),

(21) alkylcarbonyloxy groups (for example, methylcarbonyloxy, ethylcarbonyloxy and isopropylcarbonyloxy),

10 (22) cycloalkyl groups which may be substituted by a fluorine atom (for example, cyclopropyl, cyclobutyl, cyclopentyl, 2-fluorocyclopropyl, 2-fluorocyclobutyl, 3-fluorocyclobutylcyclobutyl, adamantyl and norbornyl),

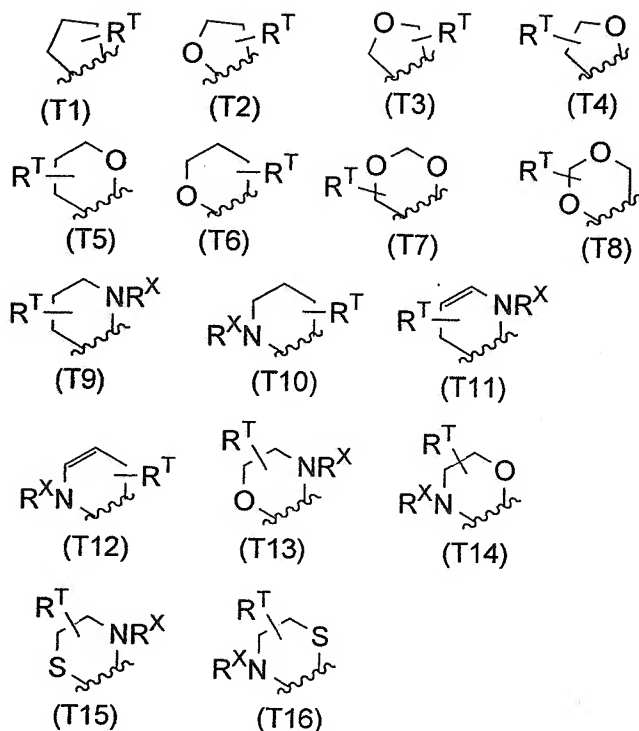
(22) cycloalkylcarbonyl groups which may be  
15 substituted by a fluorine atom (for example, cyclopropylcarbonyl, 2-fluorocyclopropylcarbonyl, cyclobutylcarbonyl and cyclopentylcarbonyl),

(23) alkylthio groups,

(24) alkylsulfinyl groups,

20 (25) optionally substituted heteroaryl groups (whose substituent(s) includes, for example, halogen atoms, alkyl groups, alkoxy groups, haloalkyl groups and haloalkoxy groups),

(26) groups represented by the following formulas (T1)  
25 to (T16):



wherein  $R^T$  is absent or one or more  $R^T$ s are present and are independently a halogen atom, a hydroxyl group, an oxo group, a carboxyl group, an optionally substituted alkyl group (whose substituent(s) includes, for

5 example, halogen atoms and alkoxy groups), an optionally substituted alkoxy carbonyl group (whose substituent(s) includes, for example, halogen atoms and alkoxy groups), an optionally substituted alkoxy group (whose substituent(s) includes, for example, halogen

10 atoms and alkoxy groups), an optionally substituted carbamoyl group (whose substituent(s) includes, for example, alkyl groups), or a saturated heterocyclic group oxycarbonyl group (the saturated heterocyclic group includes, for example, 5- or 6-membered saturated

heterocyclic groups having one or two oxygen atoms, nitrogen atoms and/or sulfur atoms, specific examples of which are tetrahydrofuranyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrothiopyranyl,

5 tetrahydrodioxothiopyranyl, pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, oxazolidinyl and thiazolidinyl), or two  $R^T$ s, when taken together, may represent methylene, ethylene, trimethylene, tetramethylenel or butenylene and may bind to one or

10 more carbon atoms constituting the ring, to form a new ring; and  $R^X$  is a hydrogen atom or an alkyl group, and (27) aroyl groups.

The substituent(s) of each of the "optionally substituted heteroaryl group", "optionally substituted

15 aralkyl group", "optionally substituted heteroarylalkyl group", "optionally substituted aroyl group", "optionally substituted heteroarylcarbonyl group", "optionally substituted aryloxy carbonyl group", "optionally substituted aryloxy group", "optionally

20 substituted aralkyloxy group", "optionally substituted heteroaryloxy group", "optionally substituted arylthio group", "optionally substituted arylsulfinyl group" and "optionally substituted arylsulfonyl group" includes those exemplified as the substituent(s) of the above-

25 mentioned "optionally substituted aryl group".

The substituent(s) of the "optionally substituted alkylcarbonyl group" includes those exemplified as the substituents of (24) the "optionally

substituted alkylcarbonyl groups" as the substituent(s) of the above-mentioned "optionally substituted alkyl group".

5       The substituent(s) of the "optionally substituted cycloalkylcarbonyl group" includes, for example, halogen atoms and alkoxy groups.

      The substituent(s) of each of the "optionally substituted alkoxy group" and the "optionally substituted alkoxy carbonyl group" includes those  
10   exemplified as the substituents of (15) the "optionally substituted alkoxy groups" as the substituent(s) of the above-mentioned "optionally substituted alkyl group".

      The substituent(s) of each of the "optionally substituted cycloalkyloxy group" and the "optionally substituted cycloalkyloxycarbonyl group" includes those  
15   exemplified as the substituents of (16) the "optionally substituted cycloalkyloxy groups" as the substituent(s) of the above-mentioned "optionally substituted alkyl group".

20       The substituent(s) of the "optionally substituted amino group" includes those exemplified as the substituents of (19) the "optionally substituted amino groups" as the substituent(s) of the above-mentioned "optionally substituted alkyl group".

25       The substituent(s) of the "optionally substituted carbamoyl group" includes, for example,  
(1) alkyl groups,  
(2) cycloalkyl groups,

(3) aryl groups which may be substituted by the following (aa), (bb), (cc) or (dd):

(aa) a halogen atom(s),

(bb) an alkoxy group which may be substituted by a halogen atom(s) (for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy, 2-fluoro-1-(fluoromethyl)ethoxy or 1-(difluoromethyl)-2,2-difluoroethoxy),

(cc) an alkyl group which may be substituted by a halogen atom(s) (for example, methyl, ethyl, propyl, isopropyl, butyl, methyl, ethyl, propyl, isopropyl, butyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2-fluoro-1-(fluoromethyl)ethyl or 1-(difluoromethyl)-2,2-difluoroethyl),

(dd) a C<sub>1-3</sub> alkylenedioxy group,

- (4) alkylsulfonyl groups,
- (5) cycloalkylsulfonyl groups,
- (6) optionally substituted arylsulfonyl groups (whose substituent(s) includes, for example, halogen atoms, alkyl groups, haloalkyl groups, alkoxy groups and haloalkoxy groups),
- (7) alkylcarbonyl groups,
- (8) alkoxycarbonyl groups,

and (9) optionally substituted aroyl groups (whose substituent(s) includes, for example, halogen atoms, alkyl groups, haloalkyl groups, alkoxy groups, haloalkoxy groups, alkoxycarbonyl groups and C<sub>1-3</sub> alkylenedioxy groups).

Specific examples of the "optionally substituted carbamoyl group" are carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, phenylcarbamoyl and phenylmethylcarbamoyl.

The two substituents of the carbamoyl group may bind to each other to form an aliphatic heterocyclic ring which may contain carbon, nitrogen, oxygen or sulfur, such as pyrrolidine, piperidine, morpholine, thiomorpholine, thiomorpholine oxide, thiomorpholine dioxide, piperazine (whose nitrogen atom may be substituted by methyl, ethyl or propyl), or the like. Specific examples the carbamoyl group are pyrrolidinocarbamoyl, piperidinocarbamoyl and morpholinocarbamoyl.

The substituent(s) of the "optionally substituted nitrogen-containing saturated heterocyclic group" includes, for example,

- (1) halogen atoms,
- (2) alkyl groups,
- (3) alkyl groups substituted by a halogen atom(s) or an alkoxy group (for example, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-

difluoroethyl, perfluoroethyl and methoxyethyl),

(4) alkoxy groups,

(5) alkoxy groups substituted by a halogen atom(s) or an alkoxy group (for example, fluoromethoxy,

5 difluoromethoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, methoxyethoxy, ethoxyethoxy, methoxypropoxy and ethoxypropoxy),

(6) cyano group,

and (7) oxo group.

10           When two  $R^7$ s,  $R^8$ s,  $R^9$ s or  $R^{10}$ s are present, they may be present on different carbon atoms, respectively.

          The phrase "two  $R^7$ s,  $R^8$ s,  $R^9$ s or  $R^{10}$ s, when taken together, represent methylene or ethylene and  
15 bind to one or more carbon atoms constituting the ring, to form a new ring" means that they form a spiro ring or bicyclo ring through one and the same carbon atom or different carbon atoms.

          The phrase "two  $R^T$ s, when taken together,  
20 represent methylene, ethylene, trimethylene, tetramethylene or butenylene and bind to one or two carbon atoms constituting the ring, to form a new ring" means that they form a spiro ring or bicyclo ring through one and the same carbon atom or different  
25 carbon atoms.

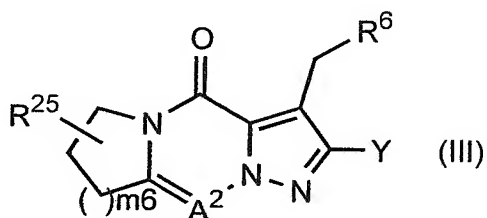
          The "haloalkoxy group" includes, for example, alkoxy groups of 1 to 4 carbon atoms substituted by a halogen atom(s). Specific examples thereof are

fluoromethoxy, difluoromethoxy and trifluoromethoxy.

The "haloalkyl group" includes, for example, alkyl groups of 1 to 4 carbon atoms substituted by a halogen atom(s). Specific examples thereof are  
 5 fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl and perfluoroethyl.

The "C<sub>1-3</sub> alkylenedioxy group" includes, for example, methylenedioxy, ethylenedioxy and trimethylenedioxy.

10 The phrase "R<sup>1</sup> and R<sup>2</sup> may be taken together with the adjacent nitrogen atom and carbon atom to form an optionally substituted 4- to 7-membered ring in the case of the solid line and dotted line between A<sup>1</sup> and A<sup>2</sup> being a double bond (A<sup>1</sup>=A<sup>2</sup>) and A<sup>1</sup> being the formula  
 15 C(R<sup>2</sup>)" means that the compound represented by the general formula (I) of the item [1] is represented by the formula (III):



wherein m<sub>6</sub> is 0, 1, 2 or 3, and R<sup>25</sup> is absent or one or two R<sup>25</sup>s are present and are independently a halogen  
 20 atom, a hydroxyl group, an oxo group, an optionally substituted alkoxy group, an optionally substituted alkyl group, an optionally substituted aryl group, an optionally substituted aralkyl group, an optionally

substituted amino group, a carboxyl group, an optionally substituted alkoxycarbonyl group or an optionally substituted carbamoyl group.

As each of the "optionally substituted amino group", "optionally substituted carbamoyl group", "optionally substituted alkylcarbonyl group", "optionally substituted phenyl group" and "optionally substituted heteroaryl group" for  $R^{13}$ , the corresponding groups explained as the substituent(s) of the above-mentioned "optionally substituted aryl group" are exemplified.

As each of the "optionally substituted carbamoyl group", "optionally substituted alkoxy group", "optionally substituted alkoxycarbonyl group", "optionally substituted aryl group", "optionally substituted aryloxycarbonyl group", "optionally substituted aroyl group", "optionally substituted heteroarylcarbonyl group" and "optionally substituted alkylcarbonyl group" for  $R^{24}$ , the corresponding groups explained as the substituent(s) of the above-mentioned "optionally substituted alkyl group" are exemplified.

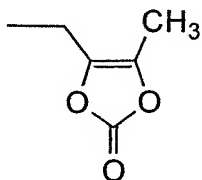
The substituent(s) of the "optionally substituted alkyl group" for  $R_c$  includes, for example, halogen atoms, alkoxy groups and cycloalkyl groups.

The substituent(s) of each of the "optionally substituted heteroaryl group" and "optionally substituted heteroaryloxy group" for  $R_c$  includes those exemplified as the substituents of (7) the "optionally

substituted heteroaryl group" as the substituent(s) of the above-mentioned "optionally substituted alkyl group".

As the "prodrug", there are exemplified those which are easily hydrolyzed in a living body to regenerate the compound (I) of the present invention. Specific examples thereof are compounds obtained by converting the amino group of the compound represented by the formula (I) to -NHQ. Here, the following are exemplified as Q:

(1)



(2)  $-\text{COR}^{20}$

(3)  $-\text{COO}-\text{CR}^{21}(\text{R}^{22})-\text{OCOR}^{23}$

(4)  $-\text{COOR}^{24}$

wherein  $\text{R}^{20}$  is a hydrogen atom, an alkyl group or an optionally substituted aryl group;  $\text{R}^{21}$  and  $\text{R}^{22}$  are independently a hydrogen atom or an alkyl group;  $\text{R}^{23}$  is a hydrogen atom, an alkyl group, an aryl group or a benzyl group; and  $\text{R}^{24}$  is an alkyl group or a benzyl group.

Preferable examples of Q are the group of (1) and the groups of (3). Preferable examples of the groups of (3) are groups in which  $\text{R}^{21}$  is a hydrogen atom,  $\text{R}^{22}$  is a hydrogen atom, methyl or ethyl and  $\text{R}^{23}$  is

a hydrogen atom, methyl or ethyl. These compounds may be produced according to conventional processes (for example, J. Med. Chem. 35, 4727 (1992) and WO 01/40180). In addition, the prodrug may be one which  
5 changes to the original compound under physiological conditions such as those described in "Development of Medicines Vol.7, Molecular Design", pp. 163-198, Hirokawa Shoten, 1990.

As the "pharmaceutically acceptable salt",  
10 there are exemplified inorganic acid salts such as hydrochloride, hydrobromide, sulfate, phosphate, nitrate, etc., and organic acid salts such as acetate, propionate, oxalate, succinate, lactate, malate, tartrate, citrate, maleate, fumarate, methanesulfonate,  
15 benzenesulfonate, p-toluenesulfonate, ascorbate, etc.

In addition, the present invention includes compounds represented by the formula (I), prodrugs thereof and pharmaceutically acceptable salts of the compounds or prodrugs. The present invention also  
20 includes their hydrates or solvates (e.g. ethanol solvate). Furthermore, the present invention includes all tautomers, all existing stereoisomers and all crystal forms of the compound (I) of the present invention.

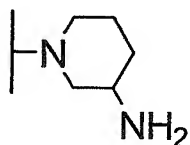
25 Examples of the compound of the present invention are given below but the compound of the present invention is not limited thereto.

Preferable examples of the bicyclic pyrazole

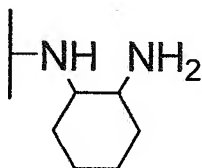
derivative of the present invention are the following bicyclic pyrazole derivatives. In the compounds listed in the following tables, the following abbreviations are used in some cases for the simplification of  
5 description.

Ph: phenyl group, Et: ethyl group, Me: methyl group, n-Pr: n-propyl group, i-Pr: isopropyl group, n-Bu: n-butyl group, t-Bu: tert-butyl group, cycpro: cyclopropyl group, cycbu: cyclobutyl group, etoet:  
10 ethoxyethyl group.

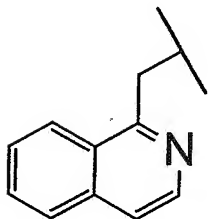
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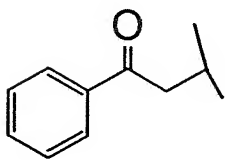
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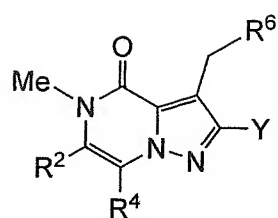


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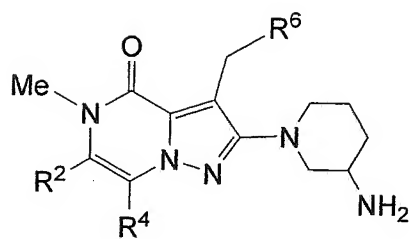


Q4:

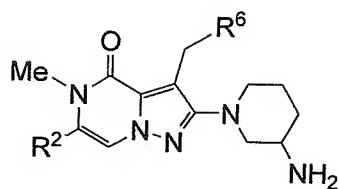




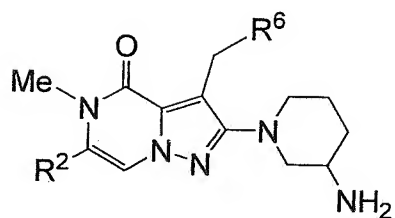
No.	R <sup>6</sup>	Y	R <sup>2</sup>	R <sup>4</sup>
1		Q1	H	H
2		Q2	H	H
3		Q1	H	H
4		Q1	H	H
5		Q1	H	H
6		Q1	H	H
7		Q1	H	H
8		Q1	H	H
9		Q1	H	H
10		Q1	H	H
11		Q1	H	H
12		Q1	Me	H
13		Q1	Me	H



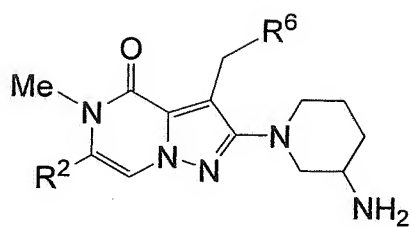
No.	R <sup>6</sup>	R <sup>2</sup>	R <sup>4</sup>	No.	R <sup>6</sup>	R <sup>2</sup>	R <sup>4</sup>
14		H	Me	21		H	CF <sub>3</sub>
15		H	Me	22		CF <sub>3</sub>	H
16		Me	Me	23		CN	H
17		Me	Et	24		C(O)Me	H
18		CF <sub>3</sub>	H	25		Et	H
19		CF <sub>3</sub>	H	26		Et	H
20		Me	CF <sub>3</sub>				



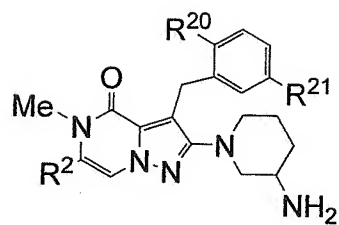
No.	R <sup>6</sup>	R <sup>2</sup>	No.	R <sup>6</sup>	R <sup>2</sup>
27		Et	40		CO <sub>2</sub> Me
28		i-Pr	41		CO <sub>2</sub> Et
29		cycpro	42		CO <sub>2</sub> Et
30		cycpro	43		C(O)NH <sub>2</sub>
31			44		C(O)NMe <sub>2</sub>
32			45		C(O)NEt <sub>2</sub>
33			46		C(O)NH <sub>2</sub>
34			47		C(O)NEt <sub>2</sub>
35			48		CN
36			49		COOH
37			50		t-BuOC(O)
38			51		
39			52		



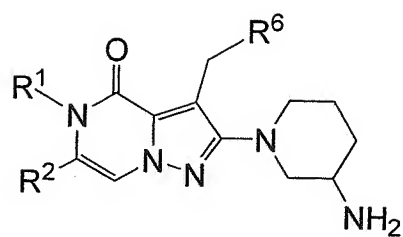
No.	R <sup>6</sup>	R <sup>2</sup>	No.	R <sup>6</sup>	R <sup>2</sup>
53			66		
54			67		
55			68		
56			69		
57			70		
58			71		
59			72		
60			73		
61			74		
62			75		
63			76		
64			77		
65			78		



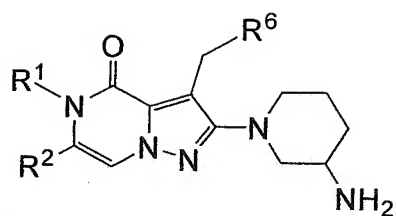
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80			93		
81			94		
82			95		
83			96		
84			97		
85			98		
86			99		
87			100		
88			101		
89			102		
90			103		
91			104		



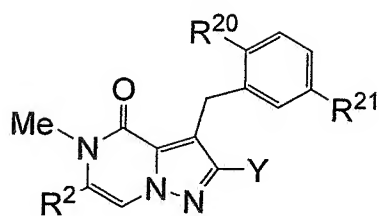
No.	R <sup>2</sup>	R <sup>20</sup>	R <sup>21</sup>	No.	R <sup>2</sup>	R <sup>20</sup>	R <sup>21</sup>
105		Cl	H	118		Cl	F
106		Cl	F	119		Me	F
107		Me	F	120		Cl	H
108		Cl	H	121		Cl	F
109		Cl	F	122		Me	F
110		Me	F	123		Me	F
111		Cl	H	124		Cl	H
112		Cl	F	125		Cl	F
113		Me	F	126		Me	F
114		Cl	H	127		Cl	H
115		Cl	F	128		Cl	F
116		Me	F	129		Cl	H
117		Cl	H	130		Cl	F



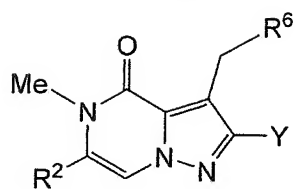
No.	R <sup>6</sup>	R <sup>2</sup>	R <sup>1</sup>
131		H	
132		Me	Q4
133		CF <sub>3</sub>	
134		C(O)Me	
135		CN	
136		CF <sub>3</sub>	
137		H	
138		CH <sub>3</sub>	
139		CN	
140		C(O)Me	
141		CN	
142		CF <sub>3</sub>	
143		H	



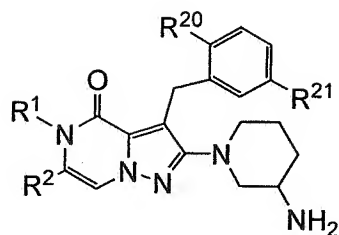
No.	R <sup>6</sup>	R <sup>2</sup>	R <sup>1</sup>
144		Me	
145		CF <sub>3</sub>	
146		C(O)Me	
147		CN	
148		CF <sub>3</sub>	
149		H	
150		Me	
151		Me	
152		C(O)Me	
153		CN	
154		CF <sub>3</sub>	
155		CN	
156		CF <sub>3</sub>	



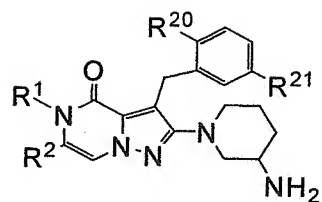
No.	R <sup>2</sup>	Y	R <sup>20</sup>	R <sup>21</sup>
157	H		Cl	H
158	Me		Cl	F
159	Et		Me	F
160	C(O)Me		Cl	H
161	CN		Cl	F
162	CF <sub>3</sub>		Me	F
163	H		Cl	H
164	Me		Cl	F
165	Et		Me	F
166	C(O)Me		Cl	H
167	CN		Cl	F
168	CF <sub>3</sub>		Me	F
169	H		Cl	H



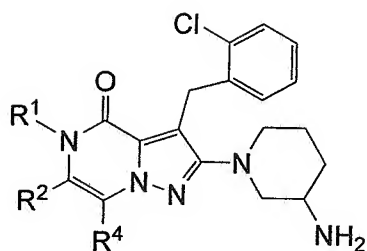
No.	R <sup>6</sup>	R <sup>2</sup>	Y	No.	R <sup>6</sup>	R <sup>2</sup>	Y
170		Me		176		Me	
171		Et		177		Me	
172		C(O)Me		178		C(O)Me	
173		CN		179		CN	
174		CF <sub>3</sub>		180		CF <sub>3</sub>	
175		H		181		CN	
				182		CF <sub>3</sub>	



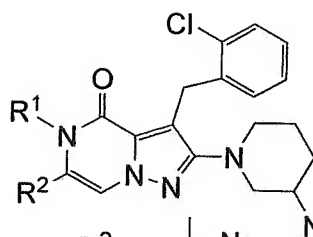
No.	R <sup>2</sup>	R <sup>1</sup>	R <sup>20</sup>	R <sup>21</sup>
183	CO <sub>2</sub> Me	H	Cl	F
184	CO <sub>2</sub> Me	CH <sub>3</sub>	Cl	F
185	CO <sub>2</sub> Et	H	Me	F
186	CO <sub>2</sub> Et	CH <sub>3</sub>	Cl	F
187	CO <sub>2</sub> Et	H	Cl	H
188	t-BuOC(O)	H	Cl	F
189	i-PrOC(O)	H	Cl	H
190	i-PrOC(O)	H	Cl	F
191	CO <sub>2</sub> Et		Cl	H
192	CO <sub>2</sub> Me	Q4	Cl	F
193	CO <sub>2</sub> Et		Cl	H
194	CO <sub>2</sub> Me		Cl	F
195	CO <sub>2</sub> Et		Cl	H



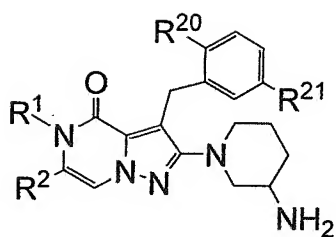
No.	R <sup>2</sup>	R <sup>1</sup>	R <sup>20</sup>	R <sup>21</sup>
196	i-PrOC(O)		Cl	H
197	CO <sub>2</sub> Me		Cl	F
198	CO <sub>2</sub> Et		Cl	H
199	CO <sub>2</sub> Me		Cl	F
200	i-PrOC(O)		Cl	H
201	CO <sub>2</sub> Et		Cl	F
202	CO <sub>2</sub> Me		Cl	F
203	i-PrOC(O)		Me	F
204	CO <sub>2</sub> Me		Cl	H
205	i-PrOC(O)		Cl	F
206	CO <sub>2</sub> Me		Cl	H
207	CO <sub>2</sub> Et		Cl	H
208	i-PrOC(O)		Cl	F



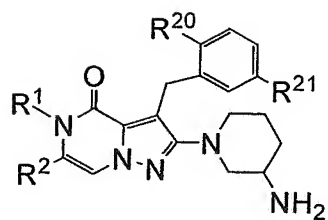
No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>4</sup>	No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>4</sup>
209	CH <sub>2</sub> CO <sub>2</sub> Me	H	H	222	CH <sub>2</sub> CO <sub>2</sub> Me		H
210	CH <sub>2</sub> CO <sub>2</sub> Me	Me	H	223	CH <sub>2</sub> CO <sub>2</sub> Me		H
211	i-PrOC(O)CH <sub>2</sub>	CN	H	224	CH <sub>2</sub> CO <sub>2</sub> Me		H
212	CH <sub>2</sub> CO <sub>2</sub> Me	CF <sub>3</sub>	H	225	CH <sub>2</sub> CO <sub>2</sub> Me	Ph	H
213	CH <sub>2</sub> CO <sub>2</sub> Et	C(O)Me	H	226	CH <sub>2</sub> CO <sub>2</sub> Et	Ph	H
214	CH <sub>2</sub> CO <sub>2</sub> H	H	H	227	Me	PhO	H
215	CH <sub>2</sub> CO <sub>2</sub> H	Me	H	228	CH <sub>2</sub> CO <sub>2</sub> Me	PhO	H
216		H	H	229	Me	PhS	H
217		Me	H	230	CH <sub>2</sub> CO <sub>2</sub> Me	PhS	H
218		Me	H	231	Me	PhS(O) <sub>2</sub>	H
219		H	H	232	CH <sub>2</sub> CO <sub>2</sub> Me	PhS(O) <sub>2</sub>	H
220		H	H	233		Me	H
221	CH <sub>2</sub> CO <sub>2</sub> Me		H	234	CH <sub>2</sub> CO <sub>2</sub> Et	Me	Me



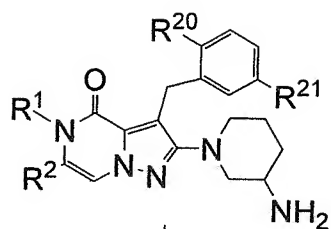
No.	R <sup>1</sup>	R <sup>2</sup>	No.	NH <sub>2</sub>	R <sup>1</sup>	R <sup>2</sup>
235	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Me	Ph	250	CH <sub>2</sub> CO <sub>2</sub> NH <sub>2</sub>	CO <sub>2</sub> Et	
236	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Me	Me	251	CH <sub>2</sub> CO <sub>2</sub> Me		
237	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Et	CN	252	CH <sub>2</sub> CO <sub>2</sub> Me		
238	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Me	CF <sub>3</sub>	253	CH <sub>2</sub> CO <sub>2</sub> Me		
239	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Me	C(O)Me	254	Ph-CH <sub>2</sub> -O-C(=O)-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>3</sub>	CO <sub>2</sub> Me	
240	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Me	H	255	CH <sub>2</sub> CO <sub>2</sub> Me	CO <sub>2</sub> NH <sub>2</sub>	
241	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Me	H	256	CH <sub>2</sub> CO <sub>2</sub> Me	CO <sub>2</sub> NMe <sub>2</sub>	
242	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Me	C(O)Ph	257	H		
243	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	Ph	258		H	
244	CH <sub>2</sub> CO <sub>2</sub> H	Ph	259		Me	
245	Me		260		Me	
246	Me					
247	Me					
248	CH <sub>2</sub> CO <sub>2</sub> Me	CO <sub>2</sub> Me				
249	CH <sub>2</sub> CO <sub>2</sub> NH <sub>2</sub>	CO <sub>2</sub> Me				



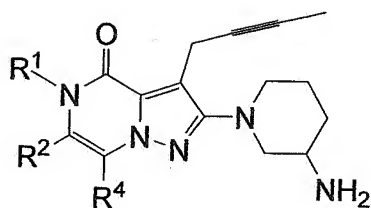
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262		Me	Cl	H
263		CN	Me	F
264		CF <sub>3</sub>	Cl	F
265		C(O)Me	Me	H
266		H	Cl	H
267		Ph	Me	F
268		Me	Cl	F
269		H	Me	H
270		CN	Cl	H
271		H	Me	F
272	H		Cl	F
273	H		Me	H



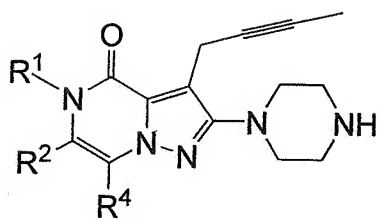
No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>20</sup>	R <sup>21</sup>
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275	Me		Cl	H
276	Me		Me	F
277	Me		Cl	F
278		CO <sub>2</sub> Me	Me	H
279		CO <sub>2</sub> Me	Cl	H
280		CO <sub>2</sub> Et	Me	F
281		CO <sub>2</sub> Me	Cl	F
282		Ph	Me	H
283		Et	Cl	H
284		CN	Me	F
285		CF <sub>3</sub>	Cl	F
286		C(O)Me	Me	H



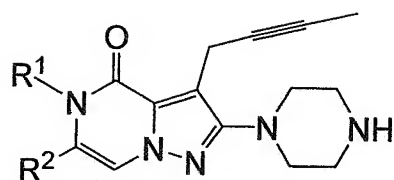
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287	CO <sub>2</sub> Me	H	Me	H	314	CO <sub>2</sub> Me	H	Br	F
288	COOH	H	Me	H	315	COOH	Me	Br	F
289	CO <sub>2</sub> Et	Me	Me	H	316	CO <sub>2</sub> Et	Me	Br	F
290	COOH	H	Cl	F	317	COOH	H	Cl	Cl
291	COOH	H	Cl	H	318	CO <sub>2</sub> Me	H	Cl	Cl
292	COOH	H	CN	H	319	COOH	H	Me	Cl
293	CO <sub>2</sub> Me	H	CN	H	320	CO <sub>2</sub> Me	H	Me	Cl
294	COOH	H	CN	F	321	COOH	H	CN	Cl
295	CO <sub>2</sub> Et	H	CN	F	322	CO <sub>2</sub> Me	H	CN	Cl
296	COOH	H	OMe	H	323	COOH	H	OMe	Cl
297	CO <sub>2</sub> Me	H	OMe	H	324	CO <sub>2</sub> Me	H	OMe	Cl
298	COOH	H	OMe	F	325	CO <sub>2</sub> Et	H	OMe	Cl
299	CO <sub>2</sub> Me	H	OMe	F	326	CO <sub>2</sub> cycpro	H	Cl	F
300	COOH	Me	CF <sub>3</sub>	H	327	CO <sub>2</sub> cycbu	H	Cl	F
301	i-PrOC(O)	H	CF <sub>3</sub>	H	328	CO <sub>2</sub> CH(Et)(Me)	H	Cl	F
302	COOH	H	CF <sub>3</sub>	F	329	CO <sub>2</sub> CH <sub>2</sub> cycpro	H	Cl	F
303	CO <sub>2</sub> Me	H	CF <sub>3</sub>	F	330	CO <sub>2</sub> CH <sub>2</sub> CH(Me) <sub>2</sub>	H	Cl	F
304	COOH	H	CF <sub>3</sub>	Cl	331	CO <sub>2</sub> Et	H	OMe	F
305	CO <sub>2</sub> Me	H	CF <sub>3</sub>	Cl	332	i-PrOC(O)	H	OMe	F
306	COOH	H	CHF <sub>2</sub>	H	333	CO <sub>2</sub> cycpro	H	OMe	F
307	CO <sub>2</sub> Et	H	CHF <sub>2</sub>	H	334	CO <sub>2</sub> CH <sub>2</sub> CH(Me) <sub>2</sub>	H	OMe	F
308	COOH	H	OCHF <sub>2</sub>	H	335	CO <sub>2</sub> Et	H	OMe	H
309	CO <sub>2</sub> Me	H	OCHF <sub>2</sub>	H	336	i-PrOC(O)	H	OMe	H
310	COOH	H	Br	H	337	CO <sub>2</sub> cycpro	H	OMe	H
311	CO <sub>2</sub> Me	H	Br	H	338	CO <sub>2</sub> CH <sub>2</sub> CH(Me) <sub>2</sub>	H	OMe	H
312	CO <sub>2</sub> Et	H	Br	H					
313	COOH	H	Br	F					



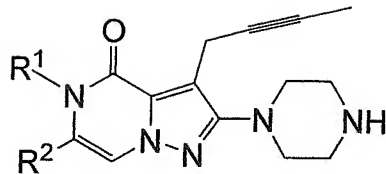
No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>4</sup>	No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>4</sup>
339		COOH	H	350		CO <sub>2</sub> Et	H
340		CO <sub>2</sub> Me	H	351		COOH	H
341		COOH	H	352		COOH	H
342		CO <sub>2</sub> Et	H	353	Q3	CN	etoet
343		COOH	H	354	Q4	COOH	H
344		CO <sub>2</sub> Me	H	355	Q4	CO <sub>2</sub> Me	H
345		CN	etoet	356	Q4	CN	etoet
346		CN	H	357	Q3	COOH	H
347		COOH	H	358	Q3	CO <sub>2</sub> Me	H
348		COOH	H	359		CN	etoet
349		CO <sub>2</sub> Me	H	360		COOH	H
				361		CO <sub>2</sub> Me	H



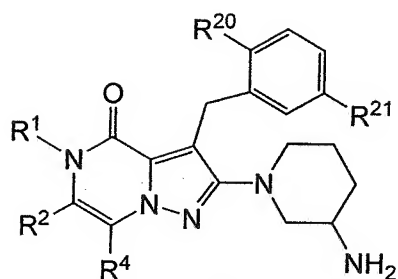
No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>4</sup>	No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>4</sup>
362		CN	etoet	374		CN	H
363		COOH	H	375	Q4	COOH	etoet
364		CO <sub>2</sub> Me	H	376	Q4	CO <sub>2</sub> Et	etoet
365		CN	etoet	377	Q3	COOH	etoet
366		COOH	H	378	Q3	CO <sub>2</sub> Et	etoet
367		CO <sub>2</sub> Me	H	379	Q3	H	H
368		CN	etoet	380		H	H
369		COOH	H	381	Q4	CN	etoet
370		CO <sub>2</sub> Me	H	382	Q4	C(O)Me	H
371		CN	H	383	Q4	H	etoet
372		COOH	H	384	Q3	H	etoet
373		CO <sub>2</sub> Me	H	385		H	etoet



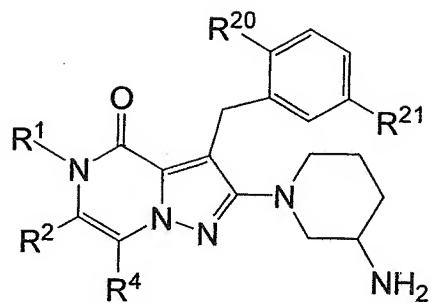
No.	R <sup>1</sup>	R <sup>2</sup>	No.	R <sup>1</sup>	R <sup>2</sup>
386		COOH	397		CO <sub>2</sub> Et
387		CO <sub>2</sub> Me	398		COOH
388		COOH	399		COOH
389		CO <sub>2</sub> Et	400	Q4	CN
390		COOH	401	Q4	COOH
391		CO <sub>2</sub> Me	402	Q4	CO <sub>2</sub> Me
392		CN	403	Q4	CN
393		CN	404	Q3	COOH
394		COOH	405	Q3	CO <sub>2</sub> Me
395		COOH	406		CN
396		CO <sub>2</sub> Me	407		COOH
			408		CO <sub>2</sub> Me



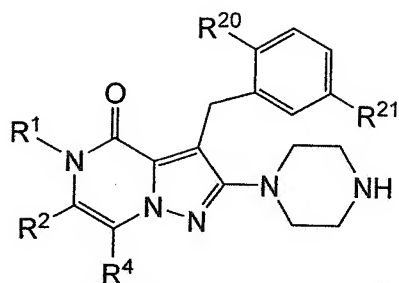
No.	R <sup>1</sup>	R <sup>2</sup>	No.	R <sup>1</sup>	R <sup>2</sup>
409	Ph(CH <sub>2</sub> ) <sub>2</sub>	CN	421	Q4	Me
410	Ph(CH <sub>2</sub> ) <sub>2</sub>	COOH	422	Q3	etoet
411	Ph(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> Me	423	Q4	Me
412		CN	424	Q3	etoet
413		i-PrOC(O)	425	Q3	C(O)Me
414		CO <sub>2</sub> Et	426	Q4	CF <sub>3</sub>
415		CN	427	Q3	CF <sub>3</sub>
416		COOH	428	Q4	CHF <sub>2</sub>
417		CO <sub>2</sub> Et	429	Q4	
418		CN	430		CN
419		i-PrOC(O)	431	Q4	C(O)Ph
420		COOH	432	Q3	cycpro



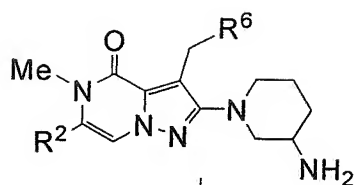
No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>4</sup>	R <sup>20</sup>	R <sup>21</sup>
433	H	CO <sub>2</sub> Me	Cl	Cl	F
434		CO <sub>2</sub> Me	Cl	Cl	F
435	H	COOH	Cl	Cl	F
436		COOH	Cl	Cl	F
437	Q3	CO <sub>2</sub> Me	Me	CN	H
438	Q3	CO <sub>2</sub> Me	Me	Cl	F
439	H	CO <sub>2</sub> Me	Me	Cl	F
440		CN	Cl	Cl	F
441	H	COOH	etoet	Cl	F
442	H	CO <sub>2</sub> Et	etoet	Cl	F
443	H	COOH	etoet	OMe	H
444	H	CO <sub>2</sub> Et	etoet	OMe	H
445	H	CN	etoet	Cl	F



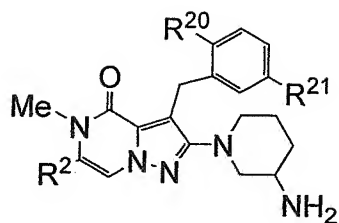
No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>4</sup>	R <sup>20</sup>	R <sup>21</sup>
446	H	CO <sub>2</sub> Me	CH <sub>2</sub> CO <sub>2</sub> Me	Cl	F
447		CO <sub>2</sub> Me	CH <sub>2</sub> CO <sub>2</sub> Et	Cl	F
448	H	COOH	CH <sub>2</sub> CO <sub>2</sub> H	Cl	F
449		COOH	MeNHC(O)CH <sub>2</sub>	Cl	F
450	Me	CO <sub>2</sub> Me		CN	H
451	Q3	CO <sub>2</sub> Me		Cl	F
452	H	CO <sub>2</sub> Me		Cl	F
453		CN	CH <sub>2</sub> C(O)NHPH	Cl	F
454		COOH		Cl	F
455	Me	CO <sub>2</sub> Me	etoet	CN	H
456	Q3	CO <sub>2</sub> Me		Cl	F
457	H	CO <sub>2</sub> Me		Cl	F
458		CN		Cl	F



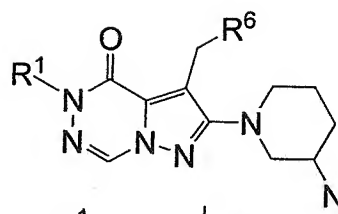
No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>4</sup>	R <sup>20</sup>	R <sup>21</sup>
459	H	CO <sub>2</sub> Me	CH <sub>2</sub> CO <sub>2</sub> Me	Cl	F
460		CO <sub>2</sub> Me	CH <sub>2</sub> CO <sub>2</sub> Et	Cl	F
461	H	COOH	CH <sub>2</sub> CO <sub>2</sub> H	Cl	F
462		COOH	CH <sub>2</sub> C(O)NHMe	Cl	F
463	Me	CO <sub>2</sub> Me		CN	H
464	Q3	CO <sub>2</sub> Me		Cl	F
465	H	CO <sub>2</sub> Me		Cl	F
466		CN	CH <sub>2</sub> C(O)NHPh	Cl	F
467		COOH		Cl	F
468	Me	CO <sub>2</sub> Me	etoet	CN	H
469	Q3	CO <sub>2</sub> Me		Cl	F
470	H	CO <sub>2</sub> Me		Cl	F
471		CN		Cl	F



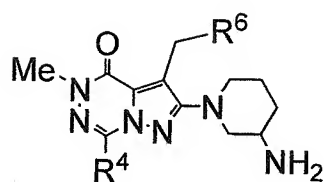
No.	R <sup>6</sup>	R <sup>2</sup>	No.	R <sup>6</sup>	R <sup>2</sup>
472		C(O)NH <sub>2</sub>	486		C(O)NMeS(O) <sub>2</sub> Me
473		C(O)NHMe	487		
474		C(O)NMe <sub>2</sub>	488		C(O)NHS(O) <sub>2</sub> Ph
475			489		
476			490		
477			491		C(O)NHC(O)Me
478			492		i-PrC(O)NHC(O)
479			493		C(O)NHCO <sub>2</sub> Et
480			494		C(O)NMeC(O)Ph
481			495		
482			496		
483			497		
484					
485		C(O)NHS(O) <sub>2</sub> Me			



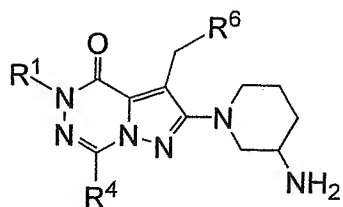
No.	R <sup>2</sup>	R <sup>20</sup>	R <sup>21</sup>	No.	R <sup>2</sup>	R <sup>20</sup>	R <sup>21</sup>
498		Cl	H	511	CH <sub>2</sub> CO <sub>2</sub> H	Cl	F
499		Cl	F	512	CH <sub>2</sub> C(O)NH <sub>2</sub>	Me	F
500		Me	F	513		Cl	H
501		Cl	H	514		Cl	F
502		Cl	F	515	i-PrOCH <sub>2</sub>	Me	F
503		Me	F	516		Me	F
504		Cl	H	517		Cl	H
505		Cl	F	518	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	Cl	F
506		Me	F	519	(CH <sub>2</sub> ) <sub>2</sub> C(O)NH <sub>2</sub>	Me	F
507		Cl	H	520	C(O)(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Et	Cl	H
508		Cl	F	521	i-PrOC(O)CH <sub>2</sub> CH <sub>2</sub>	Cl	F
509		Me	F	522	(CH <sub>2</sub> ) <sub>2</sub> C(O)Ph	Cl	H
510		Cl	H	523		Cl	F



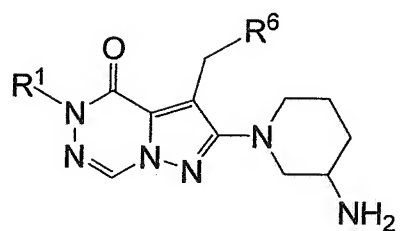
No.	R <sup>6</sup>	R <sup>1</sup>	No.	R <sup>6</sup>	R <sup>1</sup>
524		PhCH <sub>2</sub>	537		
525			538		
526			539		
527			540		
528			541		
529			542		
530		Ph(CH <sub>2</sub> ) <sub>2</sub>	543		
531			544		
532			545		
533			546		
534		Q4	547		Ph(CH <sub>2</sub> ) <sub>3</sub>
535			548		Q3
536			549		Q3



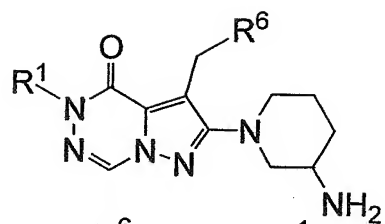
No.	R <sup>6</sup>	R <sup>4</sup>	No.	R <sup>6</sup>	R <sup>4</sup>
550		H	563		n-Pr
551		Me	564		n-Pr
552		H	565		n-Bu
553		H	566		MeO
554		Me	567		MeO
555		H	568		EtO
556		CF <sub>3</sub>	569		Me <sub>2</sub> N
557		CF <sub>3</sub>	570		Me <sub>2</sub> N
558		CF <sub>3</sub>	571		CO <sub>2</sub> Me
559		Me	572		CO <sub>2</sub> Me
560		CF <sub>3</sub>	573		CO <sub>2</sub> Et
561		Et	574		COOH
562		Et	575		COOH



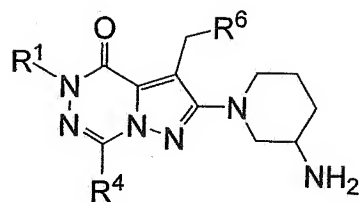
No.	R <sup>6</sup>	R <sup>4</sup>	R <sup>1</sup>	No.	R <sup>6</sup>	R <sup>4</sup>	R <sup>1</sup>
576		Me		589		CO <sub>2</sub> H	Q4
577		Me	PhC(O)CH <sub>2</sub>	590		CO <sub>2</sub> H	
578		Me		591		CO <sub>2</sub> H	Q3
579		CF <sub>3</sub>		592		CN	
580		CF <sub>3</sub>		593		CN	
581		CF <sub>3</sub>		594		CN	
582		CF <sub>3</sub>		595		CN	
583		CHF <sub>2</sub>	Q3	596		OMe	Q3
584		CHF <sub>2</sub>		597		OPh	
585		CO <sub>2</sub> Me		598		OPh	
586		CO <sub>2</sub> Me	Q4	599		OMe	
587		CO <sub>2</sub> Me		600		C(O)Me	Q3
588		CO <sub>2</sub> Et		601		C(O)Ph	



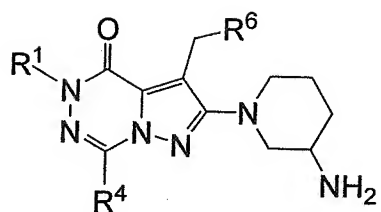
No.	R <sup>6</sup>	R <sup>1</sup>	No.	R <sup>6</sup>	R <sup>1</sup>
602			615		
603			616		
604			617		
605			618		
606			619		
607			620		
608			621		
609			622		
610			623		
611			624		
612			625		
613			626		
614			627		



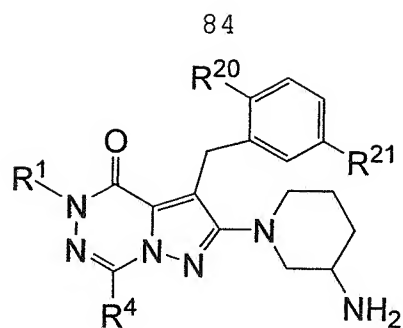
No.	R <sup>6</sup>	R <sup>1</sup>	No.	R <sup>6</sup>	R <sup>1</sup>
628			641		
629			642		
630			643		
631			644		
632			645		
633			646		
634			647		
635			648		
636			649		
637			650		
638			651		
639			652		
640			653		



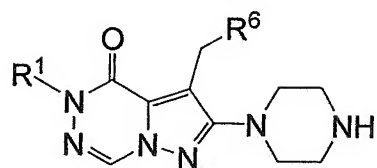
No.	R <sup>6</sup>	R <sup>4</sup>	R <sup>1</sup>
654		Me	
655		Me	
656		Me	
657		CF <sub>3</sub>	
658		CF <sub>3</sub>	Q3
659		CF <sub>3</sub>	
660		CF <sub>3</sub>	
661		CHF <sub>2</sub>	
662		CHF <sub>2</sub>	
663		CO <sub>2</sub> Me	
664		CO <sub>2</sub> Et	Q3
665		CO <sub>2</sub> H	Q3
666		CO <sub>2</sub> H	



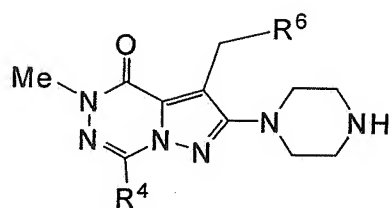
No.	R <sup>6</sup>	R <sup>4</sup>	R <sup>1</sup>
667		CH <sub>2</sub> OH	
668		CH <sub>2</sub> OMe	
669		CH <sub>2</sub> OMe	
670		CN	
671		CN	
672		CH <sub>2</sub> CO <sub>2</sub> Me	
673		CH <sub>2</sub> CO <sub>2</sub> H	Q3
674		OMe	
675		OEt	
676		OEt	
677		OPh	
678		C(O)Me	Q3
679		C(O)Ph	



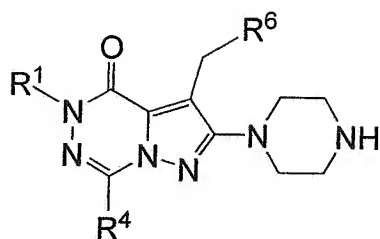
No.	R <sup>1</sup>	R <sup>4</sup>	R <sup>20</sup>	R <sup>21</sup>
680	H	CH <sub>2</sub> CO <sub>2</sub> Me	Cl	F
681	Q4	CH <sub>2</sub> CO <sub>2</sub> Et	Cl	F
682	Me	CH <sub>2</sub> CO <sub>2</sub> H	Cl	F
683		CH <sub>2</sub> C(O)NHMe	Cl	F
684			CN	H
685	Q3		Cl	F
686			Cl	F
687	(CH <sub>2</sub> ) <sub>2</sub> Ph	CH <sub>2</sub> C(O)NHPh	Cl	F
688			Cl	F
689		etoet	CN	F
690	Q3		CN	H
691			Cl	F
692			Cl	F



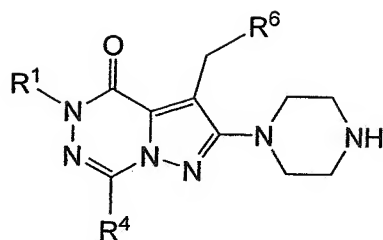
No.	R <sup>6</sup>	R <sup>1</sup>	No.	R <sup>6</sup>	R <sup>1</sup>
693		PhCH <sub>2</sub>	706		
694			707		
695			708		
696			709		
697			710		
698			711		
699		Ph(CH <sub>2</sub> ) <sub>2</sub>	712		
700			713		
701			714		
702			715		
703		PhC(O)CH <sub>2</sub>	716		Ph(CH <sub>2</sub> ) <sub>3</sub>
704			717		Q3
705			718		Q3



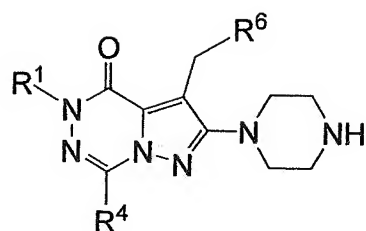
No.	R <sup>6</sup>	R <sup>4</sup>	No.	R <sup>6</sup>	R <sup>4</sup>
719		H	732		CH <sub>2</sub> CO <sub>2</sub> Me
720		H	733		CH <sub>2</sub> CO <sub>2</sub> Me
721		Me	734		CH <sub>2</sub> CO <sub>2</sub> Et
722		Me	735		CH <sub>2</sub> CO <sub>2</sub> H
723		CF <sub>3</sub>	736		CH <sub>2</sub> C(O)NHMe
724		CF <sub>3</sub>	737		
725		OMe	738		
726		OMe	739		etoet
727		CO <sub>2</sub> Me	740		
728		CO <sub>2</sub> Me	741		
729		CO <sub>2</sub> Et	742		
730		CO <sub>2</sub> H	743		
731		CO <sub>2</sub> H	744		



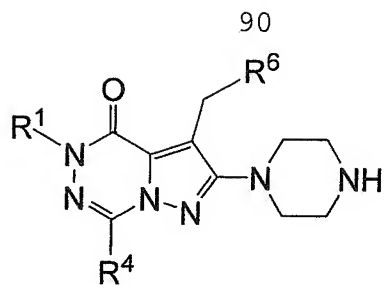
No.	R <sup>6</sup>	R <sup>4</sup>	R <sup>1</sup>
745		Me	
746		Me	Q4
747		CF <sub>3</sub>	
748		CF <sub>3</sub>	
749		CO <sub>2</sub> Me	
750		CO <sub>2</sub> Me	
751		CO <sub>2</sub> Et	
752		CO <sub>2</sub> H	Q3
753		CN	
754		OMe	
755		OPh	Q4
756		C(O)Me	
757		C(O)Ph	



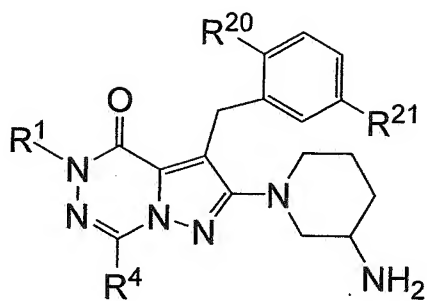
No.	R <sup>6</sup>	R <sup>4</sup>	R <sup>1</sup>
758		CH <sub>2</sub> CO <sub>2</sub> Me	Q4
759		CH <sub>2</sub> CO <sub>2</sub> Me	
760		CH <sub>2</sub> CO <sub>2</sub> Et	Q3
761		CH <sub>2</sub> CO <sub>2</sub> H	
762		CH <sub>2</sub> CO <sub>2</sub> H	
763		CH <sub>2</sub> C(O)NHMe	
764			
765			PhC(O)CH <sub>2</sub>
766		etoet	
767			
768			
769			Q3
770			



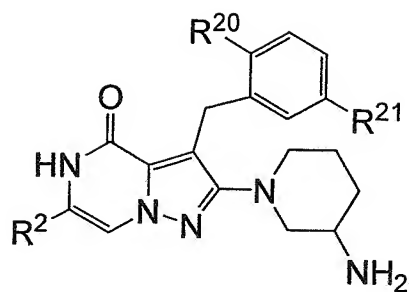
No.	R <sup>6</sup>	R <sup>4</sup>	R <sup>1</sup>
771		Me	
772		Me	
773		CF <sub>3</sub>	
774		CF <sub>3</sub>	
775		CO <sub>2</sub> Me	Q3
776		CO <sub>2</sub> Me	
777		CO <sub>2</sub> Et	
778		CO <sub>2</sub> H	
779		CN	
780		OMe	
781		OPh	Q3
782		C(O)Me	Q3
783		C(O)Ph	



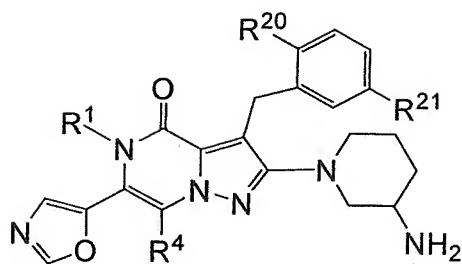
No.	R <sup>6</sup>	R <sup>4</sup>	R <sup>1</sup>
784		CH <sub>2</sub> CO <sub>2</sub> Me	
785		CH <sub>2</sub> CO <sub>2</sub> Me	
786		CH <sub>2</sub> CO <sub>2</sub> Et	
787		CH <sub>2</sub> CO <sub>2</sub> H	
788		CH <sub>2</sub> CO <sub>2</sub> H	
789		CH <sub>2</sub> C(O)NH <sub>2</sub>	
790			Q3
791			
792		etoet	
793			
794			
795			Q3
796			

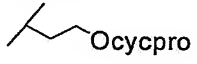
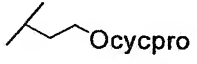
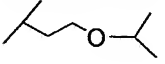
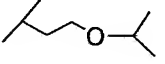
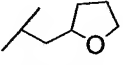
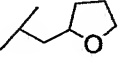


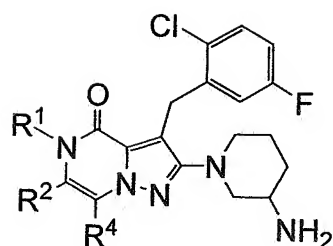
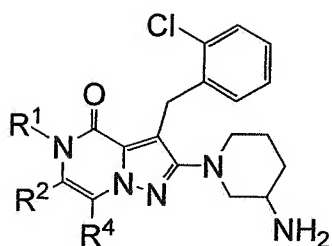
No.	R <sup>1</sup>	R <sup>4</sup>	R <sup>20</sup>	R <sup>21</sup>	No.	R <sup>1</sup>	R <sup>4</sup>	R <sup>20</sup>	R <sup>21</sup>
797	H	H	CN	H	813	Q4	etoet	Cl	F
798	Me	H	CN	H	814	Q3	etoet	Cl	F
799	Me	Me	CN	H	815	H	H	Me	H
800	Me	etoet	CN	H	816	Me	H	Me	H
801	Q4	H	CN	H	817	Me	Me	Me	H
802	Q3	H	CN	H	818	Me	etoet	Me	H
803	Q4	etoet	CN	H	819	Q4	H	Me	H
804	Q3	etoet	CN	H	820	Q3	H	Me	H
805	H	H	OMe	H	821	Q4	etoet	Me	H
806	Me	H	OMe	H	822	Q3	etoet	Me	H
807	Me	Me	OMe	H	823	Me	Me	Me	F
808	Me	etoet	OMe	H	824	Me	etoet	Me	F
809	Q4	H	OMe	H	825	Q4	H	Me	F
810	Q3	H	OMe	H	826	Q3	H	Me	F
811	Q4	etoet	OMe	H	827	Q4	etoet	Me	F
812	Q3	etoet	OMe	H	828	Q3	etoet	Me	F



No.	R <sup>2</sup>	R <sup>20</sup>	R <sup>21</sup>	No.	R <sup>2</sup>	R <sup>20</sup>	R <sup>21</sup>
829	CO <sub>2</sub> Ph	Cl	F	850	CO <sub>2</sub> CH <sub>2</sub> Ph	OMe	H
830	CO <sub>2</sub> CH <sub>2</sub> Ph	Me	F	851	t-BuOC(O)	OMe	H
831	t-BuOC(O)	Me	H	852	CO <sub>2</sub> Ph	OMe	H
832	i-PrOC(O)	Me	H	853	n-PrOC(O)	OMe	H
833	CO <sub>2</sub> Ph	Me	H	854	C(O)OCH(Me)(Et)	OMe	H
834	CO <sub>2</sub> CH <sub>2</sub> Ph	Me	H	855	C(O)OCH <sub>2</sub> cycpro	OMe	H
835	CO <sub>2</sub> Et	Me	H	856	n-PrOC(O)	CN	H
836	C(O)Ocycpro	Me	H	857	t-BuOC(O)	CN	H
837	C(O)OCH(Me)(Et)	Me	H	858	i-PrOC(O)	CN	H
838	C(O)OCH <sub>2</sub> CH(Me) <sub>2</sub>	Me	H	859	CO <sub>2</sub> Ph	CN	H
839	C(O)OCH <sub>2</sub> cycpro	Me	H	860	CO <sub>2</sub> Me	CN	F
840	CO <sub>2</sub> H	Me	F	861	CO <sub>2</sub> Et	CN	H
841	t-BuOC(O)	Me	F	862	C(O)Ocycpro	CN	H
842	i-PrOC(O)	Me	F	863	C(O)OCH(Me)(Et)	CN	H
843	CO <sub>2</sub> Ph	Me	F	864	C(O)OCH <sub>2</sub> CH(Me) <sub>2</sub>	CN	H
844	CO <sub>2</sub> Me	Me	F	865	C(O)OCH <sub>2</sub> cycpro	CN	H
845	CO <sub>2</sub> Et	Me	F	866	C(O)OCH <sub>2</sub> cycbu	Me	H
846	C(O)Ocycpro	Me	F	867	C(O)OCH <sub>2</sub> cycbu	Me	F
847	C(O)OCH(Me)(Et)	Me	F	868	C(O)OCH <sub>2</sub> cycbu	CN	H
848	C(O)OCH <sub>2</sub> CH(Me) <sub>2</sub>	Me	F	869	C(O)OCH <sub>2</sub> cycbu	OMe	H
849	C(O)OCH <sub>2</sub> cycpro	Me	F				

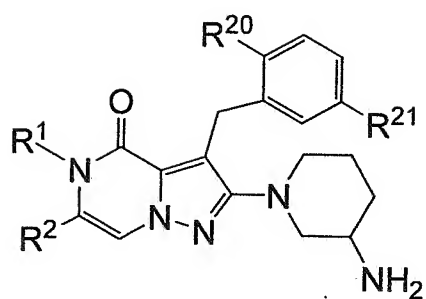


No.	R <sup>1</sup>	R <sup>4</sup>	R <sup>20</sup>	R <sup>21</sup>	No.	R <sup>1</sup>	R <sup>4</sup>	R <sup>20</sup>	R <sup>21</sup>
870	H	H	Cl	F	884	H	Me	Cl	F
871	Me	H	CN	F	885	Me	Me	Cl	F
872	H	H	MeO	H	886	H	(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>2</sub> CHF <sub>2</sub>	Cl	F
873	Me	H	MeO	H	887	Me	(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>2</sub> CHF <sub>2</sub>	Cl	F
874	Q3	H	Cl	F	888	H	 Ocycpro	Cl	F
875	Q4	H	Cl	F	889	Me	 Ocycpro	Cl	F
876	H	H	CN	H	890	H	(CH <sub>2</sub> ) <sub>2</sub> OMe	Cl	F
877	Me	H	CN	H	891	Me	(CH <sub>2</sub> ) <sub>2</sub> OMe	Cl	F
878	H	H	MeO	F	892	H		Cl	F
879	Me	H	MeO	F	893	Me		Cl	F
880	Me	etoet	Cl	F	894	H	etoet	Me	H
881	Me		Cl	F	895	Me	etoet	Me	H
882	H	etoet	Cl	F	896	H	etoet	Me	F
883	H		Cl	F	897	Me	etoet	Me	F
					898	H	H	Me	H
					899	Me	H	Me	H

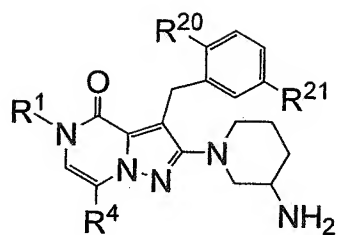


No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>4</sup>
900	H	CO <sub>2</sub> Et	CH <sub>2</sub> CO <sub>2</sub> Me
901	Me	CO <sub>2</sub> Et	CH <sub>2</sub> CO <sub>2</sub> Me
902	Me	CO <sub>2</sub> Et	CH <sub>2</sub> CO <sub>2</sub> Et
903	H	i-PrOC(O)	CH <sub>2</sub> CO <sub>2</sub> Me
904	H	i-PrOC(O)	CH <sub>2</sub> CO <sub>2</sub> Et
905	H	i-PrOC(O)	i-PrOC(O)CH <sub>2</sub>
906	Me	i-PrOC(O)	CH <sub>2</sub> CO <sub>2</sub> Me
907	Me	i-PrOC(O)	CH <sub>2</sub> CO <sub>2</sub> Et
908	Me	i-PrOC(O)	i-PrOC(O)CH <sub>2</sub>
909	H	Δ-OC(O)	CH <sub>2</sub> CO <sub>2</sub> Me
910	H	Δ-OC(O)	CH <sub>2</sub> CO <sub>2</sub> Et
911	H	Δ-OC(O)	i-PrOC(O)CH <sub>2</sub>
912	Me	Δ-OC(O)	CH <sub>2</sub> CO <sub>2</sub> Me
913	Me	Δ-OC(O)	CH <sub>2</sub> CO <sub>2</sub> Et
914	Me	Δ-OC(O)	i-PrOC(O)CH <sub>2</sub>
915	H	CO <sub>2</sub> Me	Δ-OC(O)CH <sub>2</sub>
916	H	CO <sub>2</sub> Et	Δ-OC(O)CH <sub>2</sub>
917	H	i-PrOC(O)	Δ-OC(O)CH <sub>2</sub>
918	Me	CO <sub>2</sub> Me	Δ-OC(O)CH <sub>2</sub>
919	Me	CO <sub>2</sub> Et	Δ-OC(O)CH <sub>2</sub>
920	Me	i-PrOC(O)	Δ-OC(O)CH <sub>2</sub>
921	H	CO <sub>2</sub> Et	CH <sub>2</sub> CO <sub>2</sub> Et
922	Me	CO <sub>2</sub> Me	CH <sub>2</sub> CO <sub>2</sub> Me
923	Me	CO <sub>2</sub> H	CH <sub>2</sub> CO <sub>2</sub> H
924	H	CO <sub>2</sub> H	CH <sub>2</sub> CO <sub>2</sub> H

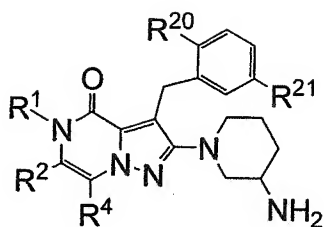
No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>4</sup>
925	H	CO <sub>2</sub> Et	CH <sub>2</sub> CO <sub>2</sub> Me
926	Me	CO <sub>2</sub> Et	CH <sub>2</sub> CO <sub>2</sub> Me
927	Me	CO <sub>2</sub> Et	CH <sub>2</sub> CO <sub>2</sub> Et
928	H	i-PrOC(O)	CH <sub>2</sub> CO <sub>2</sub> Me
929	H	i-PrOC(O)	CH <sub>2</sub> CO <sub>2</sub> Et
930	H	i-PrOC(O)	i-PrOC(O)CH <sub>2</sub>
931	Me	i-PrOC(O)	CH <sub>2</sub> CO <sub>2</sub> Me
932	Me	i-PrOC(O)	CH <sub>2</sub> CO <sub>2</sub> Et
933	Me	i-PrOC(O)	i-PrOC(O)CH <sub>2</sub>
934	H	Δ-OC(O)	CH <sub>2</sub> CO <sub>2</sub> Me
935	H	Δ-OC(O)	CH <sub>2</sub> CO <sub>2</sub> Et
936	H	Δ-OC(O)	i-PrOC(O)CH <sub>2</sub>
937	Me	Δ-OC(O)	CH <sub>2</sub> CO <sub>2</sub> Me
938	Me	Δ-OC(O)	CH <sub>2</sub> CO <sub>2</sub> Et
939	Me	Δ-OC(O)	i-PrOC(O)CH <sub>2</sub>
940	H	CO <sub>2</sub> Me	Δ-OC(O)CH <sub>2</sub>
941	H	CO <sub>2</sub> Et	Δ-OC(O)CH <sub>2</sub>
942	H	i-PrOC(O)	Δ-OC(O)CH <sub>2</sub>
943	Me	CO <sub>2</sub> Me	Δ-OC(O)CH <sub>2</sub>
944	Me	CO <sub>2</sub> Et	Δ-OC(O)CH <sub>2</sub>
945	Me	i-PrOC(O)	Δ-OC(O)CH <sub>2</sub>
946	H	CO <sub>2</sub> Et	CH <sub>2</sub> CO <sub>2</sub> Et
947	Me	CO <sub>2</sub> Me	CH <sub>2</sub> CO <sub>2</sub> Me
948	Me	CO <sub>2</sub> H	CH <sub>2</sub> CO <sub>2</sub> H



No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>20</sup>	R <sup>21</sup>	No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>2</sup>	R <sup>21</sup>
949	Q4	CN	Cl	H	965	Q4	C(O)Me	Cl	H
950	Q4	CN	Cl	F	966	Q4	C(O)Me	Cl	F
951	Q4	CN	OMe	H	967	Q4	C(O)Me	OMe	H
952	Q4	CN	CN	H	968	Q4	C(O)Me	CN	H
953	Q4	CN	Me	H	969	Q4	C(O)Me	Me	H
954	Q4	CN	OMe	F	970	Q4	C(O)Me	OMe	F
955	Q4	CN	CN	F	971	Q4	C(O)Me	CN	F
956	Q4	CN	Me	F	972	Q4	C(O)Me	Me	F
957	Q3	CN	Cl	H	973	Q3	C(O)Me	Cl	H
958	Q3	CN	Cl	F	974	Q3	C(O)Me	Cl	F
959	Q3	CN	OMe	H	975	Q3	C(O)Me	OMe	H
960	Q3	CN	CN	H	976	Q3	C(O)Me	CN	H
961	Q3	CN	Me	H	977	Q3	C(O)Me	Me	H
962	Q3	CN	OMe	F	978	Q3	C(O)Me	OMe	F
963	Q3	CN	CN	F	979	Q3	C(O)Me	CN	F
964	Q3	CN	Me	F	980	Q3	C(O)Me	Me	F

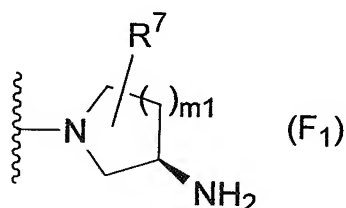


No.	R <sup>1</sup>	R <sup>4</sup>	R <sup>20</sup>	R <sup>21</sup>
981	Q4	etoet	Cl	H
982	Q4	etoet	Cl	F
983	Q4	etoet	OMe	H
984	Q4	etoet	CN	H
985	Q4	etoet	Me	H
986	Q4	etoet	OMe	F
987	Q4	etoet	CN	F
988	Q3	etoet	Cl	H
989	Q3	etoet	Cl	F
990	Q3	etoet	OMe	H
991	Q3	etoet	CN	H
992	Q3	etoet	Me	H
993	Q3	etoet	OMe	F
994	Q3	etoet	CN	F
995	Q3		Cl	H
996	Q4		Cl	F
997	Q3		Cl	H
998	Q4		Cl	F
999	Q3		Cl	H
1000	Q4		Cl	F
1001	Q4		Cl	F
1002	Q3		Cl	F



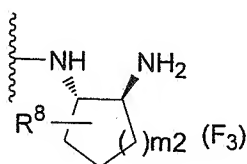
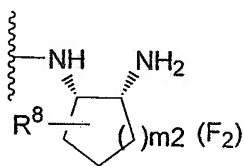
No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>4</sup>	R <sup>20</sup>	R <sup>21</sup>
1003	Q4	CN	H	Cl	H
1004	Q4	C(O)Me	H	Cl	F
1005	Q4	CN	H	OMe	H
1006	Q4	C(O)Me	H	CN	H
1007	Q4	CN	H	Me	H
1008	Q4	C(O)Me	H	OMe	F
1009	Q4	CN	H	CN	F
1010	Q3	CN	H	Cl	H
1011	Q3	C(O)Me	H	Cl	F
1012	Q3	CN	H	OMe	H
1013	Q3	C(O)Me	H	CN	H
1014	Q3	CN	H	Me	H
1015	Q3	C(O)Me	H	OMe	F
1016	Q3	CN	H	CN	F
1017	Q4	CN	etoet	Cl	H
1018	Q4	C(O)Me	etoet	Cl	F
1019	Q4	CO <sub>2</sub> Et	etoet	Cl	F
1020	Q4	C(O)Me	i-PrO(CH <sub>2</sub> ) <sub>2</sub>	Cl	H
1021	Q4	CN	cycproO(CH <sub>2</sub> ) <sub>2</sub>	Cl	F
1022	Q4	C(O)Me		Cl	F
1023	Q4	CN	etoet	CN	H
1024	Q4	C(O)Me	etoet	Me	H
1025	Q4	CO <sub>2</sub> Et	etoet	OMe	H
1026	Q3	CN	etoet	Cl	H
1027	Q3	C(O)Me	etoet	Cl	F
1028	Q3	CO <sub>2</sub> Et	etoet	Cl	F
1029	Q3	CN	etoet	CN	H
1030	Q3	C(O)Me	etoet	Me	H
1031	Q3	CO <sub>2</sub> Et	etoet	OMe	H
1032	Q4	CO <sub>2</sub> H	etoet	Cl	F
1033	Q4	CO <sub>2</sub> H	etoet	OMe	H
1034	Q3	CO <sub>2</sub> H	etoet	Cl	F
1035	Q3	CO <sub>2</sub> H	etoet	OMe	H

When in the above compounds having compound numbers 1 to 1035, the portion corresponding to Y described in the item [1] is an unsubstituted or substituted 3-aminopyrrolidin-1-yl group, an  
 5 unsubstituted or substituted 3-aminopiperidin-1-yl group or an unsubstituted or substituted (3-amino)hexahydroazepin-1-yl group, bicyclic pyrazole derivatives whose amino group at the 3-position has an absolute configuration represented by the following  
 10 formula (F<sub>1</sub>) are more preferable.



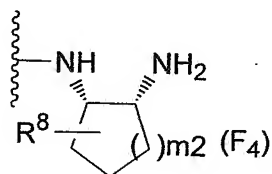
In the above formula, m and R<sup>7</sup> are as defined in the item [1].

When in the above compounds having compound numbers 1 to 1035, the portion corresponding to Y  
 15 described in the item [1] is an unsubstituted or substituted (2-aminocycloalkyl)amino group, bicyclic pyrazole derivatives whose amino groups at the 1-position and 2-position have an absolute configuration represented by the following formula (F<sub>2</sub>) or (F<sub>3</sub>) are  
 20 more preferable.



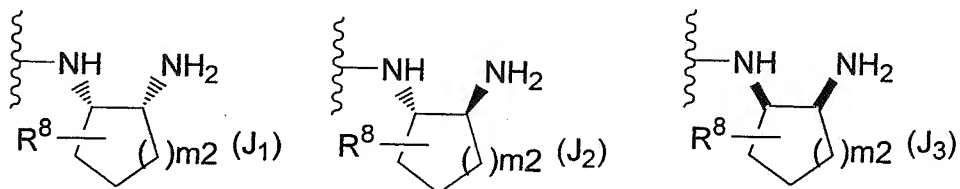
In the above formulas,  $m_2$  and  $R^8$  are as defined in the item [1].

Bicyclic pyrazole derivatives whose amino groups at the 1-position and 2-position have an  
5 absolute configuration represented by the following formula ( $F_4$ ) are still more preferable.



In the above formula,  $m_2$  and  $R^8$  are as defined in the item [1].

In the following description, a bond shown by  
10 a wedge-shaped solid line or dotted line as in the formula ( $J_1$ ) and formula ( $J_2$ ) indicates the absolute configuration of an amino group, and a bond shown by a thick line as in the formula ( $J_3$ ) indicates the relative configuration of an amino group (for example, the  
15 formula ( $J_3$ ) represents a (+)-cis form).



In the above formulas,  $m_2$  and  $R^8$  are as defined in the item [1].

In the compounds among the above compounds having compound numbers 1 to 1035, in which each of the  
20 portions corresponding to  $R^1$ ,  $R^2$  and  $R^4$ , respectively,

described in the item [1] is "an optionally substituted alkoxy carbonyl group", "an optionally substituted cycloalkoxy carbonyl group", "an optionally substituted aryloxy carbonyl group" or "an optionally substituted aralkyloxy carbonyl group", each of these substituents is changed to "a carboxyl group" in some cases under physiological conditions in a living body by oxidation, reduction, hydrolysis or the like by an enzyme, or hydrolysis by acid in the stomach, or the like.

10           A process for producing the compound represented by the formula (I) of the present invention is explained below with reference to examples, which should not be construed as limiting the scope of the invention. In the present specification, the following  
15   abbreviations are used in some cases for the simplification of description.

Boc: tert-butoxycarbonyl group

Cbz: benzyloxycarbonyl group

TBS: tert-butyldimethylsilyl group

20   MOM: methoxymethyl group

Ph: phenyl group

Bn: benzyl group

Et: ethyl group

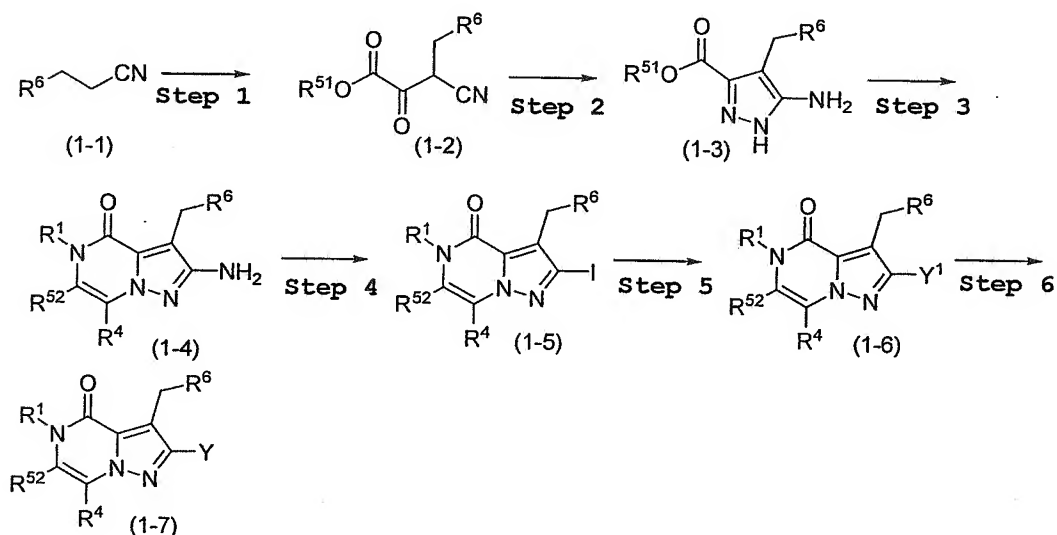
Me: methyl group

25           The bicyclic pyrazole derivative represented by the formula (I) may be synthesized from a well-known compound by a combination of well-known synthesis processes. It may be synthesized, for example, by any

of the following processes.

### Production Process 1

A compound of the formula (1-7) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

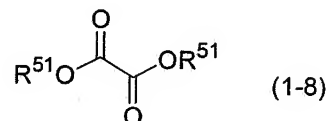


wherein  $R^1$ ,  $R^4$ ,  $R^6$  and  $Y$  are as defined in the item [1];  $R^{51}$  is an alkyl group;  $R^{52}$  is "a hydrogen atom", "an optionally substituted alkyl group", "an optionally substituted alkoxy carbonyl group", "an optionally substituted aryloxy carbonyl group", "an optionally substituted cycloalkyl group", "an optionally substituted aryl group", "an optionally substituted aralkyl group", "an optionally substituted heteroarylalkyl group" or "an optionally substituted heteroaryl group", which is represented by  $R^2$  described in the item [1]; and  $Y^1$  is a group formed by protecting

the NH or NH<sub>2</sub> of Y with a protective group.

1) Step 1

A compound (1-2) may be produced by reacting a compound (1-1) with a compound (1-8) represented by the formula:



wherein R<sup>51</sup> is as defined above, in an inert solvent in the presence of a base. The base includes sodium ethoxide, sodium methoxide, potassium tert-butoxide, sodium hydride and the like. A preferable example thereof is sodium ethoxide. The amount of the base used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (1-1). The amount of the compound (1-8) used is usually chosen in the range of 0.5 to 3 equivalents per equivalent of the compound (1-1). The inert solvent includes, for example, alcohol solvents (e.g. methanol, ethanol and 2-propanol), ether solvents (tetrahydrofuran and 1,4-dioxane), and mixed solvents thereof. When sodium ethoxide is used as the base, ethanol is preferable as the inert solvent. The reaction temperature may be chosen in the range of about 50°C to about 100°C. Sodium ethoxide may be produced from sodium and ethanol chosen as the inert solvent.

2) Step 2

A compound (1-3) is produced by reacting the

compound (1-2) with hydrazine monohydrate in an inert solvent. The amount of hydrazine monohydrate used is usually chosen in the range of 1 to 3 equivalents per equivalent of the compound (1-2). The inert solvent includes, for example, alcohol solvents (e.g. methanol, ethanol and 2-propanol), acetic acid, and mixed solvents thereof. The reaction temperature is chosen in the range of about 50°C to about 120°C, and the reaction is usually carried out with refluxing.

10 3) Step 3

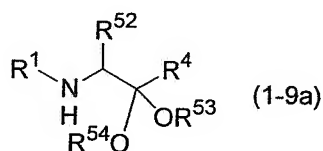
A compound (1-4) may be produced from the compound (1-3) by carrying out the following reactions (1) to (4).

(1) The compound (1-3) is reacted with di-  
15 tert-butyl dicarbonate in an inert solvent in the presence of a base. The amount of di-tert-butyl dicarbonate used is usually chosen in the range of 3 to 6 equivalents per equivalent of the compound (1-3). The inert solvent includes ether solvents  
20 (tetrahydrofuran and 1,4-dioxane). The reaction temperature is chosen in the range of about -10°C to about 40°C.

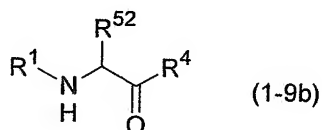
(2) The product obtained in the above item (1) is reacted in an inert solvent in the presence of a  
25 base. The base includes sodium hydroxide, potassium hydroxide, lithium hydroxide and the like. The amount of the base used is usually chosen in the range of 3 to 10 equivalents. The inert solvent includes mixed

solvents of water and alcohol solvents (e.g. methanol, ethanol and 2-propanol). The volume ratio of water to the alcohol is chosen in the range of 0.5 to 1.0. The reaction temperature is chosen in the range of about  
 5 40°C to about 80°C.

(3) The product obtained in the above item (2) is reacted with a compound (1-9a) represented by the formula:



wherein  $\text{R}^1$ ,  $\text{R}^4$  and  $\text{R}^{52}$  are as defined above, and each of  
 10  $\text{R}^{53}$  and  $\text{R}^{54}$ , which are the same, is methyl, ethyl or isopropyl, or  $\text{R}^{53}$  and  $\text{R}^{54}$ , when taken together, may form ethylene or trimethylene, or  
 a compound (1-9b) represented by the formula:



wherein  $\text{R}^1$ ,  $\text{R}^4$  and  $\text{R}^{52}$  are as defined above, in an inert  
 15 solvent by the use of a condensing agent optionally in the presence of a base. As the compound (1-9b), a commercial reagent may be used, or the compound (1-9b) may be produced by converting the ester portion of the compound (12-8) described hereinafter in the production  
 20 process 12 to a carboxylic acid by the method described in the step 3, (2) in the production process 1, and converting the carboxylic acid to a ketone by the

method described in the step 1 to step 2 in the production process 9 described hereinafter. As the compound (1-9a), a commercial reagent may be used, or the compound (1-9a) may be produced from the compound  
5 (1-9b) by the same production process as described in literature (for example, Tetrahedron 50, 6299 (1994) and R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., 1989).

The base is not particularly limited so long  
10 as it is used as a base in a usual reaction. The base includes, for example, organic bases such as 1-hydroxybenzotriazole, N-methylmorpholine, triethylamine, diisopropylethylamine, tributylamine, 1,8-diazabicyclo[5,4,0]undec-7-ene, 1,5-  
15 diazabicyclo[4,3,0]nona-5-ene, 1,4-diazabicyclo[5,4,0]undec-7-ene, pyridine, dimethylaminopyridine, picoline, etc., and inorganic bases such as sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium  
20 carbonate, sodium hydroxide, sodium hydride, etc. As the condensing agent, those described in Japanese Chemical Association, Jikken Kagaku Koza (Experimental Chemistry) Vol. 22, Maruzen Co., Ltd. are exemplified. The condensing agent includes, for example, phosphoric  
25 esters such as diethyl cyanophosphate, diphenylphosphorylazide, etc.; carbodiimides such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, dicyclohexylcarbodiimide, etc.;

combinations of a disulfide (e.g. 2,2'-dipyridyl disulfide) and a phosphine (e.g. triphenylphosphine); phosphorus halides such as N,N'-bis(2-oxo-3-oxazolidinyl)phosphinic chloride, etc.; combinations of  
5 an azodicarboxylic acid diester (e.g. diethyl azodicarboxylate) and a phosphine (e.g. triphenylphosphine); and 2-halo-1-lower-alkylpyridinium halides such as 2-chloro-1-methylpyridinium iodide, etc. The inert solvent includes, for example, ether  
10 solvents such as tetrahydrofuran, diethyl ether, 1,4-dioxane, 1,2-dimethoxyethane, etc.; hydrocarbon solvents such as hexane, heptane, toluene, benzene, xylene, etc.; halogenated hydrocarbon solvents such as dichloromethane, chloroform, 1,2-dichloroethane, etc.;  
15 ketone solvents such as acetone, etc.; and aprotic solvents such as acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide, hexamethylenephosphoamide, etc. Mixed solvents of these solvents may also be used as the inert solvent. The reaction temperature is chosen  
20 in the range of about -70°C to about 80°C.

A production example in this step is described below. The product obtained in the above item (2) is reacted with the compound of the formula (1-9a) or the formula (1-9b) in an inert solvent in the  
25 presence of 1-hydroxybenzotriazole by using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride as a condensing agent. The inert solvent includes dimethylformamide, ether solvents (e.g. tetrahydrofuran

and 1,4-dioxane) and halogenated hydrocarbon solvents (e.g. dichloromethane and 1,2-dichloroethane). A preferable example thereof is dimethylformamide. The reaction temperature is chosen in the range of about -  
5 10°C to about 40°C.

(4) The product obtained in the above item (3) is reacted in an inert solvent in the presence of an acid. The acid includes hydrochloric acid, phosphoric acid, sulfuric acid and the like. A  
10 preferable example thereof is hydrochloric acid. The amount of the acid used is usually chosen in the range of 10 to 20 equivalents. The inert solvent includes ethers (e.g. tetrahydrofuran and 1,4-dioxane). A preferable example thereof is 1,4-dioxane. In  
15 addition, 1,4-dioxane containing hydrogen chloride may be used as the solvent. The reaction temperature is chosen in the range of about -10°C to about 100°C.

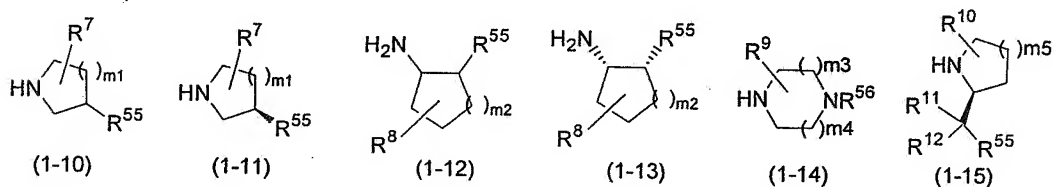
#### 4) Step 4

A compound (1-5) is produced by reacting the  
20 compound (1-4) with diiodomethane and isoamyl nitrite in an inert solvent. The amount of diiodomethane used is usually chosen in the range of 10 to 50 equivalents per equivalent of the compound (1-4). Diiodomethane may be used also as a solvent. The amount of isoamyl  
25 nitrite used is usually chosen in the range of 1 to 10 equivalents per equivalent of the compound (1-4). The inert solvent includes hydrocarbon solvents such as toluene, benzene, xylene, etc.; and halogenated

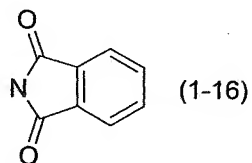
hydrocarbon solvents such as dichloromethane, chloroform, 1,2-dichloroethane, etc. The reaction temperature is chosen in the range of about 20°C to about 40°C.

# 5) Step 5

A compound (1-6) is produced by reacting the compound (1-5) with a compound selected from a compound (1-10), a compound (1-11), a compound (1-12), a compound (1-13), a compound (1-14) and a compound (1-15) represented by the formulas:



wherein m1, m2, m3, m4, m5, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup> are as defined in the item [1], R<sup>55</sup> is N=C(Ph)<sub>2</sub>, NHBoc, NHCbz or the following formula (1-16):



and R<sup>56</sup> is Boc or Cbz, in an inert solvent in the presence of potassium phosphate, ethylene glycol and copper iodide. The amount of the compound (1-10), compound (1-11), compound (1-12), compound (1-13), compound (1-14) or compound (1-15) used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (1-5). The amount of

potassium phosphate used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (1-5). The amount of ethylene glycol used is usually chosen in the range of 1 to 5 equivalents per  
5 equivalent of the compound (1-5). The amount of copper iodide used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (1-5). The inert solvent includes, for example, alcohol solvents (e.g. methanol, ethanol and 2-propanol). The reaction  
10 temperature is chosen in the range of about 50°C to about 150°C. It is also possible to carry out the reaction in a closed reaction vessel such as an autoclave.

The compound (1-11) and the compound (1-13)  
15 may be produced by the process described hereinafter as production process 23 and the process described hereinafter as production process 24, respectively. The compound (1-14) may be produced by the process described in literature (for example, Synthesis 391  
20 (1994), Org. Lett. 5, 1591 (2003), Synthesis 1065 (1992), Synlett 755 (2002), J. Org. Chem. 56, 3063 (1991), J. Org. Chem. 60, 4177 (1995) and J. Org. Chem. 57, 6653 (1992)) or the process described hereinafter as production process 25. The compound (1-10) may be  
25 produced by the process described hereinafter as production process 22 or the process described in literature (for example, US5232929). The compound (1-15) may be produced by the same process as that

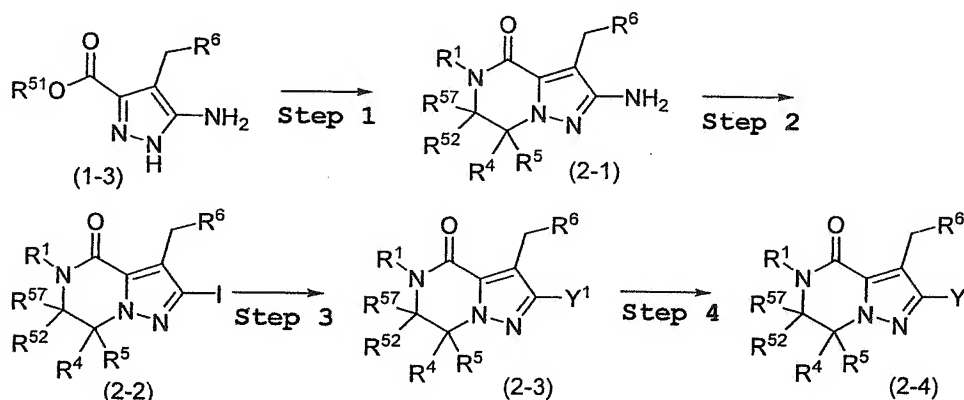
described in literature (for example, J. Org. Chem. 61, 6700 (1996)) or the like. The compound (1-12) may be produced by the same process as that described in literature (for example, US6075167) or the like.

# 5 6) Step 6

The compound (1-7) may be produced from the compound (1-6) by the same process as that described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)) or the  
10 like.

## Production Process 2

A compound of the formula (2-4) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:



15 wherein R<sup>1</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and Y are as defined in the item [1]; R<sup>51</sup>, R<sup>52</sup> and Y<sup>1</sup> are as defined in the production process 1; and R<sup>57</sup> has the same meaning as that of R<sup>52</sup> defined in the production process 1.

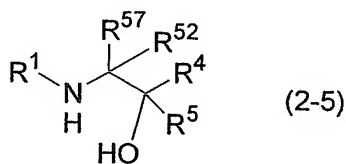
## 1) Step 1

A compound (2-1) may be produced from a compound (1-3) by carrying out the following reactions (1) to (6).

5 (1) Reaction is carried out by the same method as in the production process described in the step 3, (1) in the production process 1.

(2) Reaction is carried out by the same method as in the production process described in the  
10 step 3, (2) in the production process 1.

(3) The product obtained in the above item (2) is reacted with a compound (2-5) represented by the formula:



wherein  $R^1$ ,  $R^4$ ,  $R^5$ ,  $R^{52}$  and  $R^{57}$  are as defined above, by  
15 the same method as in the production process described in the step 3, (3) in the production process 1.

(4) The product obtained in the above item (3) is reacted with carbon tetrabromide in an inert solvent in the presence of triphenylphosphine. The  
20 amount of triphenylphosphine used is usually chosen in the range of 1 to 3 equivalents. The amount of carbon tetrabromide used is usually chosen in the range of 1 to 3 equivalents. The inert solvent includes aprotic solvents such as N,N-dimethylformamide, dimethyl

sulfoxide, and acetonitrile. The reaction temperature is chosen in the range of about  $-10^{\circ}\text{C}$  to about  $40^{\circ}\text{C}$ .

(5) A base is added to the reaction solution obtained in the above item (4) and the reaction is  
5 carried out. The base includes potassium tert-butoxide, sodium tert-butoxide, cesium carbonate, potassium carbonate, sodium carbonate, sodium hydride and the like. A preferable example thereof is potassium carbonate. The amount of the base used is  
10 chosen usually in the range of 1 to 5 equivalents. The reaction temperature may be chosen in the range of about  $30^{\circ}\text{C}$  to about  $100^{\circ}\text{C}$ .

(6) From the product obtained in the above item (5), Boc is removed by the same method as that  
15 described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)) or the like.

## 2) Step 2

A compound (2-2) may be produced from the  
20 compound (2-1) by the same production process as described in the step 4 in the production process 1.

## 3) Step 3

A compound (2-3) may be produced from the compound (2-2) by the same production process as  
25 described in the step 5 in the production process 1.

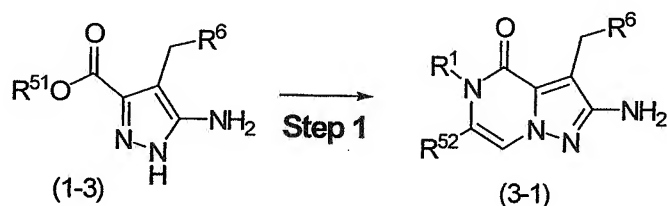
## 4) Step 4

The compound (2-4) may be produced from the compound (2-3) by the same production process as

described in the step 6 in the production process 1.

### Production Process 3

A compound (3-1) corresponding to the  
 5 compound (1-4) described in the production process 1 in  
 the case where  $R^4$  is a hydrogen atom, may be produced  
 also by the following process:



wherein  $R^1$  and  $R^6$  are as defined in the item [1], and  $R^{51}$   
 and  $R^{52}$  are as defined in the production process 1.

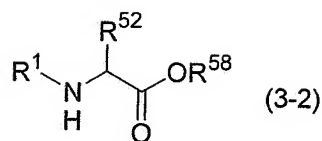
10 The compound (3-1) may be produced from a  
 compound (1-3) by carrying out the following reactions  
 (1) to (5) in the step 1.

#### 1) Step 1

(1) Reaction is carried out by the same  
 15 method as in the production process described in the  
 step 3, (1) in the production process 1.

(2) Reaction is carried out by the same  
 method as in the production process described in the  
 step 3, (2) in the production process 1.

20 (3) The product obtained in the above item  
 (2) is reacted with a compound (3-2) represented by the  
 formula:



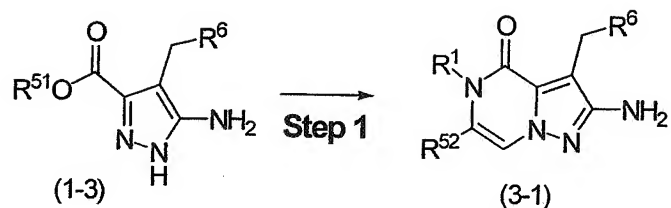
wherein  $\text{R}^1$  and  $\text{R}^{52}$  are as defined above, and  $\text{R}^{58}$  is methyl, ethyl or isopropyl, by the same method as in the production process described in the step 3, (3) in the production process 1. As the compound (3-2), a  
 5 commercial reagent may be used, or the compound (3-2) may be produced by the same process as the production process of a compound (12-8) described hereinafter in the production process 12.

(4) The product obtained in the above item  
 10 (3) is reacted with diisobutylaluminum hydride in an inert solvent. The amount of diisobutylaluminum hydride used is usually chosen in the range of 3 to 10 equivalents. The inert solvent includes toluene, xylene and ether solvents (e.g. tetrahydrofuran). A  
 15 preferable example thereof is toluene. The reaction temperature is chosen in the range of about  $-100^\circ\text{C}$  to about  $0^\circ\text{C}$ , preferably about  $-80^\circ\text{C}$  to about  $-60^\circ\text{C}$ .

(5) Reaction is carried out by the same method as in the production process described in the  
 20 step 3, (4) in the production process 1.

#### Production Process 4

The compound (3-1) described in the production process 3 may be produced also by the following process:



wherein  $R^1$  and  $R^6$  are as defined in the item [1], and  $R^{51}$  and  $R^{52}$  are as defined in the production process 1.

The compound (3-1) may be produced from a compound (1-3) by carrying out the following reactions

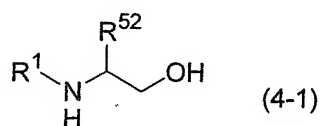
5 (1) to (5) in the step 1.

1) Step 1

(1) Reaction is carried out by the same method as in the production process described in the step 3, (1) in the production process 1.

10 (2) Reaction is carried out by the same method as in the production process described in the step 3, (2) in the production process 1.

(3) The product obtained in the above item (2) is reacted with a compound (4-1) represented by the  
15 formula:



wherein  $R^1$  and  $R^{52}$  are as defined above, by the same method as in the production process described in the step 3, (3) in the production process 1. As the compound (4-1), a commercial reagent may be used, or  
20 the compound (4-1) may be produced from the compound (12-8) described hereinafter in the production process

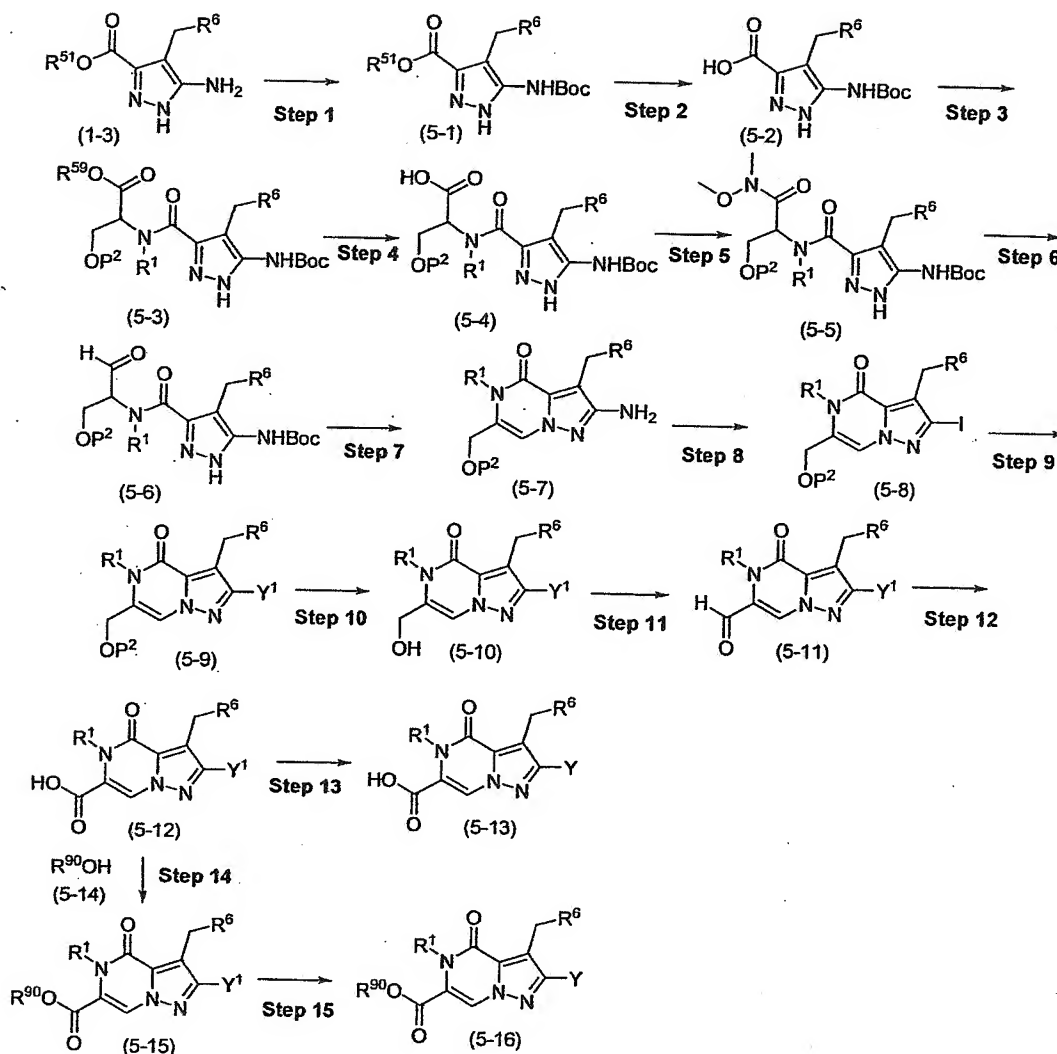
12, by the same production process as described in  
literature (for example, Synth. Commun. 33, 2907  
(2003), Synlett 37 (2002), and R.C. Ralock,  
"Comprehensive Organic transformation", VCH publisher  
5 Inc., 1989).

(4) The hydroxymethyl group of the product  
obtained in the above item (3) is converted to a formyl  
group by the same method as in the production process  
described in literature (for example, J. Am. Chem. Soc.  
10 118, 12246 (1996), J. Comb. Chem. 3, 223 (1999), J.  
Comb. Chem. 5, 516 (2002), Org. Lett. 3, 3041 (2001)  
and J. Org. Chem. 23, 7907 (2001)).

(5) Reaction is carried out by the same  
method as in the production process described in the  
15 step 3, (4) in the production process 1.

#### Production Process 5

Each of compounds of the formula (5-13) and  
the formula (5-16) as the compound of the formula (I),  
or a salt thereof is produced, for example, by the  
20 following process:



wherein  $R^1$ ,  $R^6$  and  $Y$  are as defined in the item [1];  $R^{51}$  and  $Y^1$  are as defined in the production process 1;  $R^{59}$  is methyl or ethyl;  $P^2$  is a protective group for hydroxyl group; and  $R^{90}$  is an optionally substituted alkyl group, an optionally substituted aryl group or an optionally substituted heteroaryl group.

A compound (5-1) may be produced from a compound (1-3) by carrying out the following reactions (1) to (5).

## 1) Step 1

A compound (5-1) may be produced from a compound (1-3) by the same production process as described in the step 3, (1) in the production process

5 1.

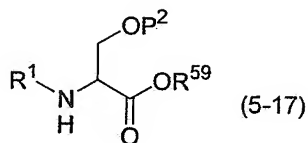
## 2) Step 2

A compound (5-2) may be produced from the compound (5-1) by the same production process as described in the step 3, (2) in the production process

10 1.

## 3) Step 3

A compound (5-3) may be produced from the compound (5-2) and a compound (5-17) represented by the formula:



15 wherein  $\text{R}^1$ ,  $\text{R}^{59}$  and  $\text{P}^2$  are as defined above, by the same production process as described in the step 3, (3) in the production process 1. Preferable examples of  $\text{P}^2$  are methoxymethyl, benzyl, p-methoxybenzyl, tert-butyltrimethylsilyl and triisopropylsilyl. As the

20 compound (5-17), a commercial reagent may be used, or the compound (5-17) may be produced by the same process as the production process of a compound (12-8) described hereinafter in the production process 12.

## 4) Step 4

A compound (5-4) may be produced from the compound (5-3) by the same production process as described in the step 3, (2) in the production process

5 1.

## 5) Step 5

A compound (5-5) may be produced from the compound (5-4) and N,O-dimethylhydroxylamine hydrochloride by the same production process as

10 described in literature (for example, Bioorg. Med. Chem. Lett. 11, 2951 (2001), Synthesis 1852 (2000), Organic Letters 2, 4091 (2000) and Bioorg. Med. Chem. Lett. 11, 287 (2001)).

## 6) Step 6

15 A compound (5-6) may be produced from the compound (5-5) by the same production process as described in literature (for example, Bioorg. Med. Chem. Lett. 13, 265 (2003), Tetrahedron Letters 40, 5179 (1999), Tetrahedron Letters 34, 7371 (1993),  
20 Tetrahedron 55, 12907 (1999), Synlett 700 (1995) and J. Org. Chem. 58, 2446 (1993)).

## 7) Step 7

A compound (5-7) may be produced from the compound (5-6) by the same production process as  
25 described in the step 3, (4) in the production process  
1.

## 8) Step 8

A compound (5-8) may be produced from the

compound (5-7) by the same production process as described in the step 4 in the production process 1.

9) Step 9

A compound (5-9) may be produced from the compound (5-8) by the same production process as described in the step 5 in the production process 1.

10) Step 10

A compound (5-10) may be produced from the compound (5-9) by the same process as that described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)) or the like.

11) Step 11

A compound (5-11) may be produced from the compound (5-10) by the same production process as described in literature (for example, J. Org. Chem. 65, 7757 (2000), Pharmazie 55, 273 (2000), Pharmazie 55, 645 (2000), J. Am. Chem. Soc. 122, 7144 (2000), Tetrahedron Lett. 36, 8513 (1995), Tetrahedron Lett. 36, 9117 (1995) and Tetrahedron Lett. 36, 8513 (1995)).

12) Step 12

A compound (5-12) may be produced from the compound (5-11) by the same production process as described in literature (for example, J. Chem. Soc. Perkin Trans. I 529 (2002), Heterocycles 32, 1933 (1991), Synthesis 295 (1993), Tetrahedron Lett. 35, 2959 (1994), Tetrahedron Lett. 40, 9085 (1999), Synthesis 1878 (1999) and Synth. Commun. 26, 2775

(1996)).

13) Step 13

The compound (5-13) may be produced from the compound (5-12) by the same production process as  
5 described in the step 6 in the production process 1.

14) Step 14

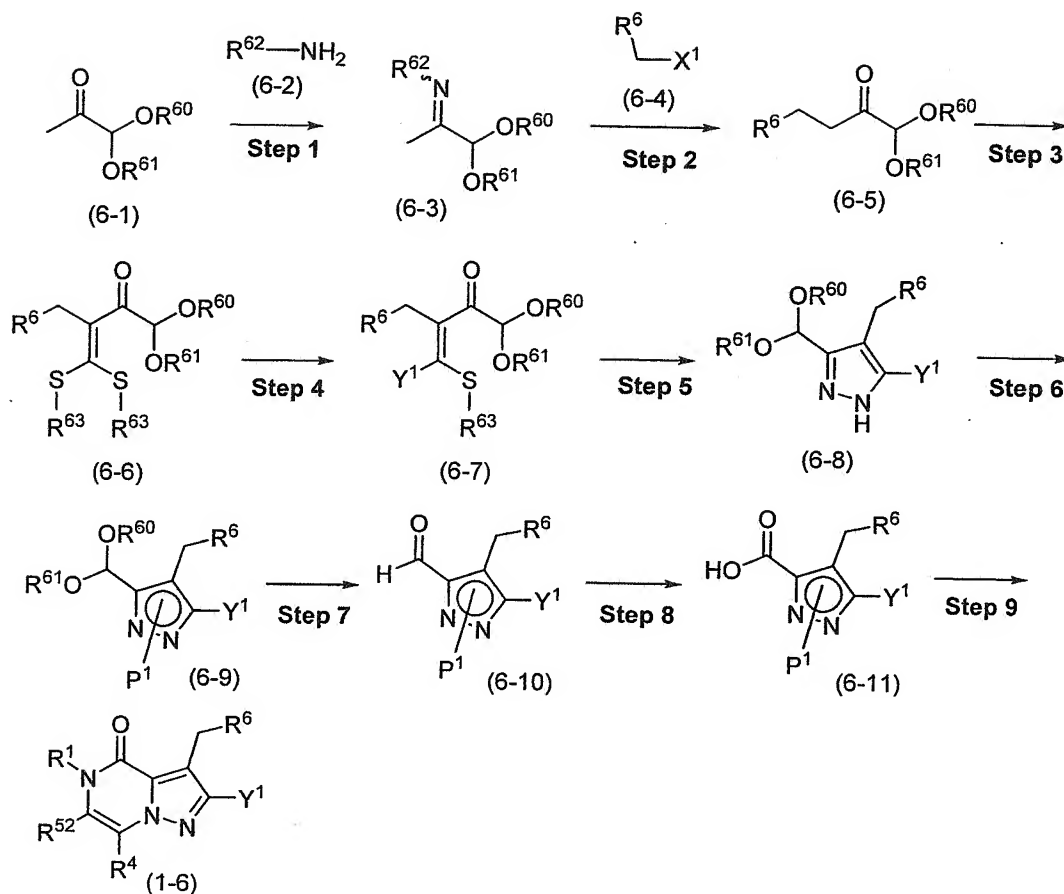
A compound (5-15) may be produced from the compound (5-12) and a compound (5-14) by the same process as that described in literature (for example,  
10 R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., (1989)) or the like.

15) Step 15

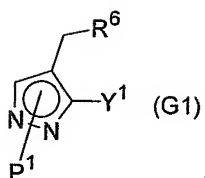
The compound (5-16) may be produced from the compound (5-15) by the same production process as  
15 described in the step 6 in the production process 1.

Production Process 6

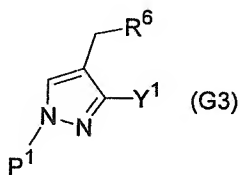
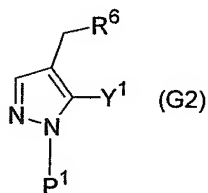
In the production process 1, the compound of the formula (1-6) or a salt thereof may be produced also by, for example, the following process:



wherein  $R^1$ ,  $R^4$  and  $R^6$  are as defined in the item [1];  $R^{52}$  and  $Y^1$  are as defined in the production process 1; each of  $R^{60}$  and  $R^{61}$ , which are the same, is methyl, ethyl or isopropyl, or  $R^{60}$  and  $R^{61}$ , when taken together, may form ethylene or trimethylene;  $X^1$  is a leaving group (for example, a bromine atom, a chlorine atom, methanesulfonyloxy, trifluoromethanesulfonyloxy or p-toluenesulfonyloxy);  $P^1$  is a protective group for nitrogen atom;  $R^{62}$  is a cycloalkyl group;  $R^{63}$  is methyl or ethyl; and the following formula (G1):



as the partial structural formula of each of the compound (6-9), compound (6-10) and compound (6-11) represents the following formula (G2) or the following formula (G3):



#### 5 1) Step 1

A compound (6-3) may be produced from a compound (6-1) by the same process as that described in literature (for example, J. Am. Chem. Soc. 125, 9900 (2003)) or the like.

#### 10 2) Step 2

A compound (6-5) may be produced from the compound (6-3) by carrying out the following reactions (1) and (2).

(1) The compound (6-3) is treated with a base in an inert solvent and reacted with a compound (6-4). The base includes lithium diisopropylamide, lithium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide and the like. The amount of the base used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (6-3). The

amount of the compound (6-4) used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (6-3). The inert solvent includes, for example, ether solvents such as diethyl ether, tetrahydrofuran, 1,4-dioxane, etc. Mixed solvents of these solvents may also be used. The reaction temperature is chosen in the range of about  $-100^{\circ}\text{C}$  to about  $20^{\circ}\text{C}$ .

(2) The product obtained in the above item (1) is reacted with an acid in an inert solvent. The acid includes inorganic acids such as hydrochloric acid, sulfuric acid, etc.; and organic acids such as trifluoroacetic acid, acetic acid, etc. The amount of the acid used is usually chosen in the range of 1 equivalent to large excess equivalents per equivalent of the product obtained in the above item (1). The inert solvent includes water, tetrahydrofuran and the like. The reaction temperature is chosen in the range of about  $0^{\circ}\text{C}$  to about  $30^{\circ}\text{C}$ .

### 3) Step 3

A compound (6-6) may be produced from the compound (6-5) by continuously carrying out the following procedures ((1) to (4)).

(1) The compound (6-5) is treated with potassium bis(trimethylsilyl)amide in an inert solvent such as tetrahydrofuran. The amount of potassium bis(trimethylsilyl)amide used is chosen in the range of 1 to 2 equivalents per equivalent of the compound (6-

5). The reaction temperature is chosen in the range of about  $-100^{\circ}\text{C}$  to about  $-50^{\circ}\text{C}$ .

(2) Carbon disulfide is added to the reaction solution obtained in the above item (1). The amount of carbon disulfide used is chosen in the range of 1 to 2 equivalents per equivalent of the compound (6-5). The reaction temperature is chosen in the range of about  $-100^{\circ}\text{C}$  to about  $-50^{\circ}\text{C}$ .

(3) Potassium bis(trimethylsilyl)amide is added to the reaction solution obtained in the above item (2). The amount of potassium bis(trimethylsilyl)amide used is chosen in the range of 1 to 2 equivalents per equivalent of the compound (6-5). The reaction temperature is chosen in the range of about  $-100^{\circ}\text{C}$  to about  $-50^{\circ}\text{C}$ .

(4) Methyl iodide or ethyl iodide is added to the reaction solution obtained in the above item (3). The amount of methyl iodide or ethyl iodide used is chosen in the range of 2 to 5 equivalents per equivalent of the compound (6-5). The reaction temperature is chosen in the range of about  $-100^{\circ}\text{C}$  to about  $40^{\circ}\text{C}$ .

#### 4) Step 4

A compound (6-7) may be produced by reacting the compound (6-6) with a compound selected from the compound (1-10), compound (1-11), compound (1-12), compound (1-13), compound (1-14) and compound (1-15) described in the step 5 in the production process 1, in

an inert solvent in the presence or absence of a base. The base includes sodium ethoxide, sodium methoxide, potassium tert-butoxide, sodium hydride and the like. The amount of the base used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (6-6). The amount of the compound (1-10), compound (1-11), compound (1-12), compound (1-13), compound (1-14) or compound (1-15) used is usually chosen in the range of 1 to 3 equivalents per equivalent of the compound (6-6). The inert solvent includes, for example, alcohol solvents such as methanol, ethanol, 2-propanol, etc.; ether solvents such as tetrahydrofuran, 1,4-dioxane, etc.; hydrocarbon solvents such as toluene, o-xylene, m-xylene, p-xylene, etc.; and aprotic solvents such as dimethylformamide, etc. The reaction temperature may be chosen in the range of about 50°C to about 180°C.

#### 5) Step 5

A compound (6-8) may be produced by reacting the compound (6-7) with hydrazine monohydrate in an inert solvent. The amount of hydrazine monohydrate used is usually chosen in the range of 1 to 3 equivalents per equivalent of the compound (6-7). The inert solvent includes, for example, alcohol solvents such as methanol, ethanol, 2-propanol, etc., and aprotic solvents such as dimethylformamide, etc. The reaction temperature is chosen in the range of about 50°C to about 150°C.

## 6) Step 6

A compound (6-9) may be produced from the compound (6-8) by the production process described in literature (for example, Protective Groups in Organic  
5 Synthesis 2nd Edition (John Wiley & Sons, Inc.)).

Preferable examples of P<sup>1</sup> are dimethylsulfamoyl group, methoxymethyl group and p-methoxybenzyl group.

## 7) Step 7

A compound (6-10) may be produced by reacting  
10 the compound (6-9) with an organic acid in an inert solvent. The organic acid includes acetic acid, propionic acid and the like. The amount of the organic acid used is usually chosen in the range of 1 equivalent to large excess equivalents per equivalent  
15 of the compound (6-9). The inert solvent includes, for example, water, dioxane and alcohol solvents (e.g. methanol, ethanol and 2-propanol). The reaction temperature is chosen in the range of about 30°C to about 100°C.

## 20 8) Step 8

A compound (6-11) may be produced from the compound (6-10) by the same process as that described in literature (for example, Tetrahedron 59, 6045 (2003)) or the like.

## 25 9) Step 9

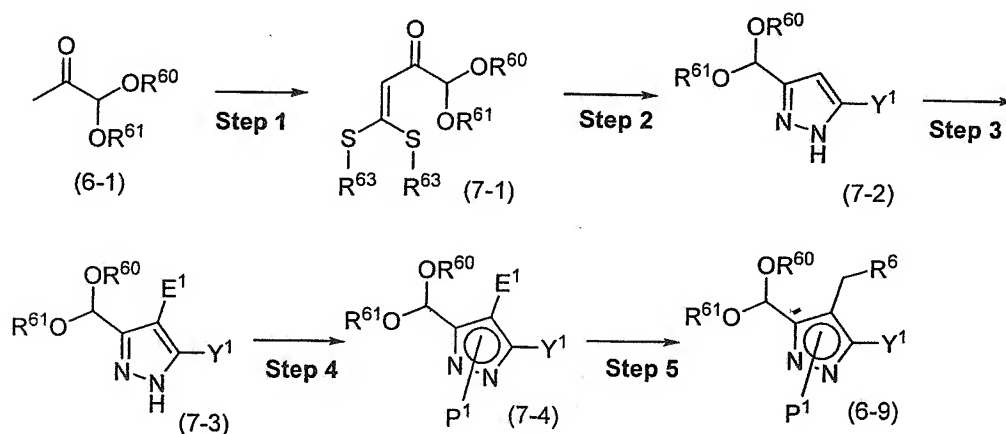
The compound (1-6) may be produced from the compound (6-11) by carrying out the following reactions (1) and (2).

(1) Reaction is carried out by the same method as in the production process described in the step 3, (3) in the production process 1.

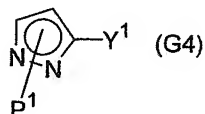
(2) Reaction is carried out by the same method as in the production process described in the step 3, (4) in the production process 1. In this reaction, a compound in which the protective group for primary amino group or secondary amino group in  $Y^1$  has been removed is produced in some cases. The primary amino group or secondary amino group in  $Y$  may be protected again with a protective group (e.g. Boc or Cbz) by the same method as in the production process described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)).

#### Production Process 7

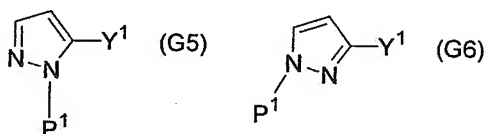
The compound of the formula (6-9) in the production process 6 or a salt thereof may be produced also by, for example, the following process:



wherein  $R^6$  is as defined in the item [1];  $Y^1$  is as defined in the production process 1;  $P^1$ ,  $R^{60}$ ,  $R^{61}$  and  $R^{63}$  are as defined in the production process 6;  $E^1$  is an iodine atom, a bromine atom or a chlorine atom; and the following formula (G4):



as the partial structural formula of each of a compound (7-4) and the compound (6-9) represents the following formula (G5) or the following formula (G6):



#### 1) Step 1

A compound (7-1) may be produced from a compound (6-1) by continuously carrying out the following procedures ((1) to (3)).

(1) The compound (6-1) is treated with, for example, an alkali metal hydride such as sodium hydride or potassium hydride in an inert solvent such as dimethylformamide or tetrahydrofuran. The amount of the alkali metal hydride used is chosen in the range of 1 to 10 equivalents per equivalent of the compound (6-1). The reaction temperature is chosen in the range of about  $-10^{\circ}\text{C}$  to about  $40^{\circ}\text{C}$ .

(2) Carbon disulfide is added to the

reaction solution obtained in the above item (1). The amount of carbon disulfide used is chosen in the range of 1 to 5 equivalents per equivalent of the compound (6-1). The reaction temperature is chosen in the range  
5 of about  $-10^{\circ}\text{C}$  to about  $50^{\circ}\text{C}$ .

(3) Methyl iodide or ethyl iodide is added to the reaction solution obtained in the above item (2). The amount of methyl iodide or ethyl iodide used is chosen in the range of 2 to 10 equivalents per  
10 equivalent of the compound (6-1). The reaction temperature is chosen in the range of about  $-10^{\circ}\text{C}$  to about  $40^{\circ}\text{C}$ .

2) Step 2

A compound (7-2) may be produced from the  
15 compound (7-1) by continuously carrying out the following procedures ((1) and (2)).

(1) Reaction is carried out by the same method as in the production process described in the step 4 in the production process 6.

20 (2) Reaction is carried out by the same method as in the production process described in the step 5 in the production process 6.

3) Step 3

A compound (7-3) may be produced by reacting  
25 the compound (7-2) with a halogen (iodine, bromine or chlorine) in an inert solvent in the presence of an inorganic base. The amount of the halogen used is usually chosen in the range of 1 to 5 equivalents per

equivalent of the compound (7-2). The inorganic base includes sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate and the like. The amount of the inorganic base used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (7-2). The inert solvent includes, for example, halogenated hydrocarbon solvents such as chloroform, dichloromethane, dichloroethane, etc. The reaction temperature is chosen in the range of about -10°C to about 40°C.

#### 4) Step 4

A compound (7-4) may be produced from the compound (7-3) by the same production process as described in the step 6 in the production process 6.

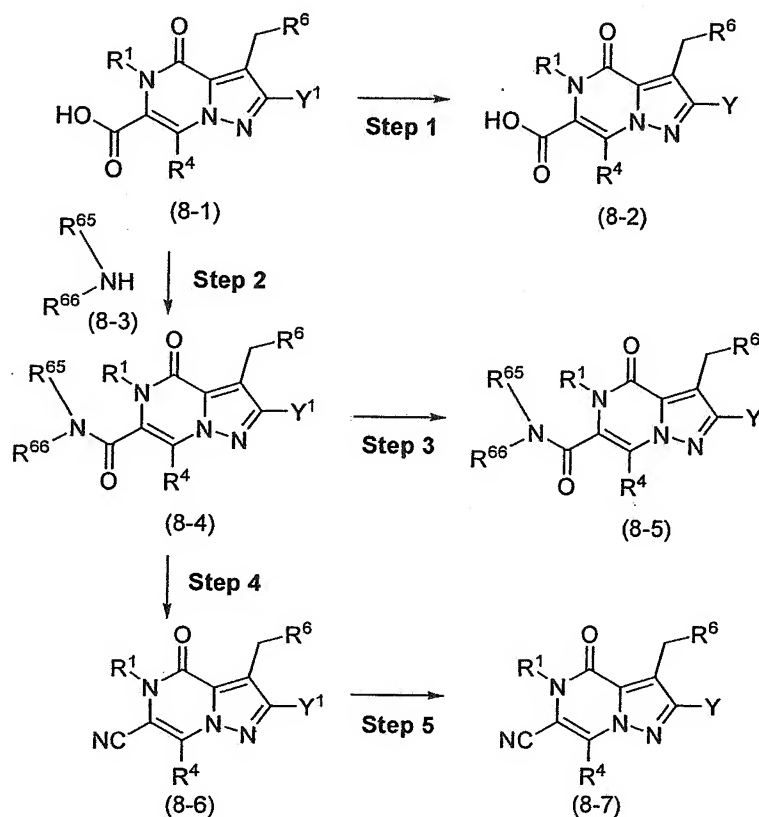
#### 5) Step 5

The compound (6-9) may be produced from the compound (7-4) by the same production process as described in literature (for example, Chem. Rev. 95, 2457 (1995), Organic Process Research & Development 5, 254 (2001), J. Med. Chem. 45, 999 (2002), Synthesis 563 (1997), J. Org. Chem. 65, 9001 (2000), J. Org. Chem. 64, 4196 (1999), J. Org. Chem. 67, 3904 (2002), Adv. Synth. Catal. 345, 620 (2003) and J. Med. Chem. 43, 675 (2000)).

### Production Process 8

Each of compounds of the formula (8-2), the

formula (8-5) and the formula (8-7) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:



wherein  $R^1$ ,  $R^4$ ,  $R^6$  and  $Y$  are as defined in the item [1];

- 5 the compound represented by the formula (8-1) corresponds to the compound (12-6) described in the production process 12 when  $R^{69}$  is a carboxyl group;  $Y^1$  is as defined in the production process 1; and  $R^{65}R^{66}NC(O)$  represents "an optionally substituted carbamoyl group" for  $R^2$  described in the item [1].

#### 1) Step 1

The compound (8-2) may be produced from the compound (8-1) by the same production process as

described in the step 6 in the production process 1.

2) Step 2

A compound (8-4) may be produced by condensing the compound (8-1) with a compound (8-3) in an inert solvent by the use of a dehydrating-  
condensation agent such as dicyclohexylcarbodiimide or carbonyldiimidazole optionally in the presence of an additive such as 4-(dimethylamino)pyridine. The inert solvent includes, for example, ether solvents such as diethyl ether, tetrahydrofuran, 1,4-dioxane, etc.; aprotic solvents such as N,N-dimethylformamide, etc.; and halogenated hydrocarbon solvents such as dichloromethane, dichloroethane, etc. Mixed solvents of these solvents may also be used. A preferable example thereof is N,N-dimethylformamide. The reaction temperature is usually chosen in the range of about 0°C to about 50°C.

3) Step 3

The compound (8-5) may be produced from the compound (8-4) by the same production process as described in the step 6 in the production process 1.

4) Step 4

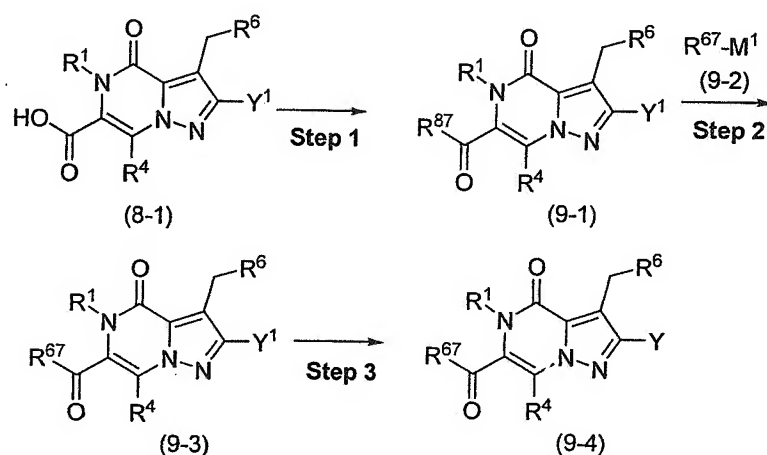
A compound (8-6) may be produced from the compound (8-4) by the same production process as described in literature (for example, R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., 1989).

5) Step 5

The compound (8-7) may be produced from the compound (8-6) by the same production process as described in the step 6 in the production process 1.

#### Production Process 9

- 5           A compound of the formula (9-4) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:



wherein  $R^1$ ,  $R^4$ ,  $R^6$  and  $Y$  are as defined in the item [1]; the formula (8-1) is as defined above;  $Y^1$  is as defined in the production process 1;  $R^{67}$  is 4-morpholinyl or  $N(CH_3)OCH_3$ ;  $R^{67}C(O)$  is "an optionally substituted aroyl group", "an optionally substituted heteroarylcarbonyl group" or "an optionally substituted alkylcarbonyl group", which is represented by  $R^2$  described in the item [1]; and  $M^1$  is lithium, magnesium chloride, magnesium bromide or magnesium iodide.

#### 1) Step 1 to Step 2

A compound (9-3) may be produced from a

compound (8-1) by the same production process as described in literature (for example, Bioorg. Med. Chem. Lett. 11, 2951 (2001), Tetrahedron Letters 42, 8955 (2001), Synthesis 1852 (2000), Organic Letters 2, 5 4091 (2000), Tetrahedron Letters 42, 5609 (2001), Synthesis 2239 (2001), Synlett 5, 715 (2002), J. Org. Chem. 67, 5032 (2002), Bioorg. Med. Chem. Lett. 11, 287 (2001), Tetrahedron Letters 42, 3763 (2001), J. Org. Chem. 67, 8938 (2002), Bioorg. Med. Chem. Lett. 12, 10 2887 (2002) and Tetrahedron Letters 43, 6313 (2002)).

As a compound (9-2), a commercial one may be used, or the compound (9-2) may be produced by the process described, for example, in Japanese Chemical Association, Jikken Kagaku Koza (Experimental 15 Chemistry) Vol. 25, Maruzen Co., Ltd.

In the step 2, anhydrous cerium(III) chloride may be added. The amount of anhydrous cerium(III) chloride used is usually chosen in the range of 1 to 5 equivalents per equivalent of a compound (9-1).

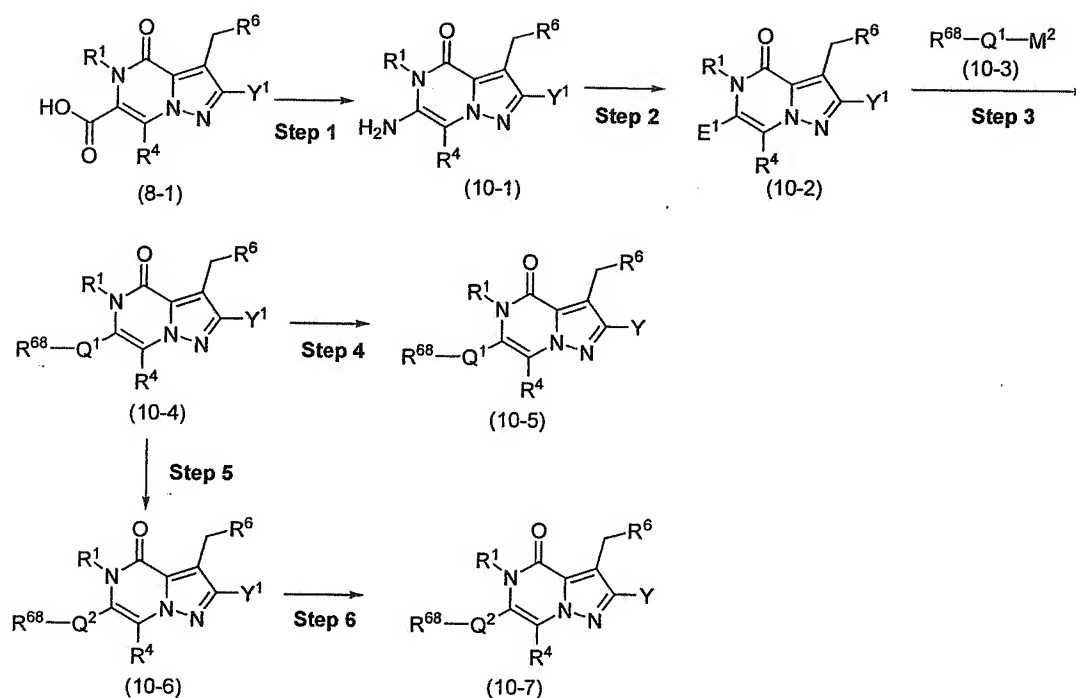
## 20 2) Step 3

The compound (9-4) may be produced from the compound (9-3) by the same production process as described in the step 6 in the production process 1.

## Production Process 10

25 Each of compounds of the formula (10-5) and the formula (10-7) as the compound of the formula (I), or a salt thereof is produced, for example, by the

following process:



wherein  $R^1$ ,  $R^4$ ,  $R^6$  and  $Y$  are as defined in the item [1];  
 $Y^1$  is as defined in the production process 1;  $R^{68}-Q^1$  is  
 "an optionally substituted alkoxy group", "an  
 5 optionally substituted aryloxy group", "an optionally  
 substituted arylthio group" or "an optionally  
 substituted heteroaryloxy group", which is represented  
 by  $R^2$  described in the item [1];  $R^{68}-Q^2$  is "an optionally  
 substituted arylsulfonyl group" represented by  $R^2$   
 10 described in the item [1];  $E^1$  is a chlorine atom, a  
 bromine atom or an iodine atom; and  $M^2$  is lithium,  
 potassium or cesium.

#### 1) Step 1

A compound (10-1) may be produced from a

compound (8-1) by the same production process as described in literature (for example, R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., 972-976 (1989) and Eur. J. Org. Chem. 1353  
5 (2000)).

2) Step 2

A compound (10-2) may be produced from the compound (10-1) by the same production process as described in literature (for example, R.C. Ralock,  
10 "Comprehensive Organic transformation", VCH publisher Inc., 1989).

3) Step 3

A compound (10-4) may be produced from the compound (10-2) by the same production process as  
15 described in literature (for example, Heterocycles 52, 253 (2000), WO95/18109 and WO00/58309).

4) Step 4

The compound (10-5) may be produced from the compound (10-4) by the same production process as  
20 described in the step 6 in the production process 1.

5) Step 5

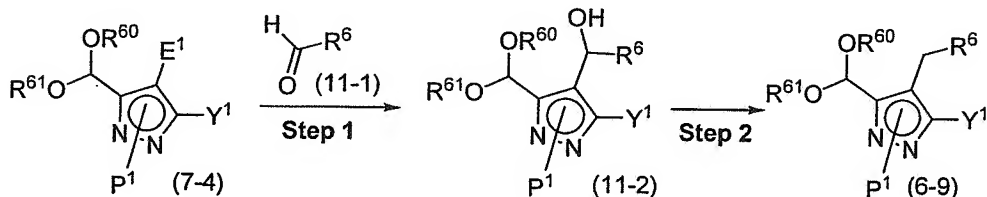
When  $Q^1$  of the compound (10-4) is a sulfur atom, a compound (10-6) obtained by converting  $Q^1$  of the compound (10-4) to sulfonyl may be produced by the same  
25 production process as described in literature (for example, R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., 1989).

6) Step 6

The compound (10-7) may be produced from the compound (10-6) by the same production process as described in the step 6 in the production process 1.

#### Production Process 11

- 5           The compound of the formula (6-9) described in the production process 7 may be produced also by, for example, the following process:



wherein  $R^6$  is as defined in the item [1];  $Y^1$  is as defined in the production process 1;  $P^1$ ,  $R^{60}$  and  $R^{61}$  are  
 10 as defined in the production process 6; and  $E^1$  is as defined in the production process 7.

#### 1) Step 1

A compound (11-2) may be produced from a compound (7-4) by the same production process as  
 15 described in literature (for example, Bioorg. Med. Chem. Lett. 8, 183 (1998) and Tetrahedron, 51, 11043 (1995)).

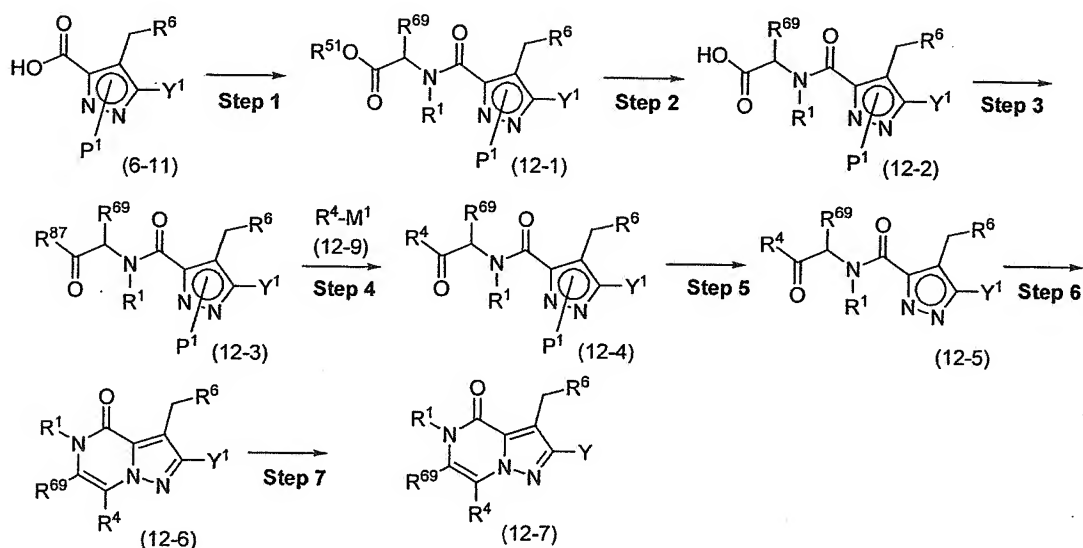
#### 2) Step 2

The compound (6-9) may be produced from the  
 20 compound (11-2) by the same production process as described in literature (for example, Bioorg. Med. Chem. Lett. 8, 183 (1998), Tetrahedron, 51, 11043

(1995), Tetrahedron, 57, 4817 (2001), Tetrahedron Lett. 42, 1073 (2001) and Bioorg. Med. Chem. Lett. 12, 2643 (2002)).

## Production Process 12

- 5                    A compound of the formula (12-7) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:

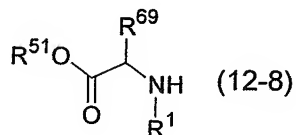


- wherein  $R^1$ ,  $R^4$ ,  $R^6$  and  $Y$  are as defined in the item [1];  
 $Y^1$  and  $R^{51}$  are as defined in the production process 1;  
 10  $R^{87}$  and  $M^1$  are as defined in the production process 9;  
 $R^{69}$  is "a hydrogen atom", "an optionally substituted alkyl group", "an optionally substituted cycloalkyl group", "a carboxyl group", "an optionally substituted alkoxy carbonyl group", "an optionally substituted aryl group",  
 15 "an optionally substituted aryloxy carbonyl group", "an optionally substituted aralkyl group", "an

optionally substituted aroyl group", "an optionally substituted heteroaryl group", "an optionally substituted heteroarylalkyl group", "an optionally substituted heteroarylcarbonyl group" or "an optionally substituted alkylcarbonyl group", which is represented by  $R^2$  described in the item [1]; and  $P^1$  is as defined in the production process 6.

1) Step 1

A compound (12-1) may be produced by reacting a compound (6-11) with a compound represented by the formula:



wherein  $R^1$ ,  $R^{51}$  and  $R^{69}$  are as defined above, by the same method as in the production process described in the step 3, (3) in the production process 1. As the compound (12-8), a commercial reagent may be used, or the compound (12-8) may be produced by the process described in literature (for example, Chem. Rev. 103, 3013 (2003), Chem. Rev. 103, 2795 (2003), Acc. Chem. Res. 36, 342 (2003), Acc. Chem. Res. 36, 10 (2003), J. Heterocyclic Chemistry 39, 437 (2002) and R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., 1989).

2) Step 2

A compound (12-2) may be produced from the compound (12-1) by the same production process as

described in the step 3, (2) in the production process  
1.

3) Step 3 to Step 4

A compound (12-4) may be produced from the  
5 compound (12-2) by the same production process as  
described in the step 1 to step 2 in the production  
process 9.

4) Step 5

A compound (12-5) may be produced from the  
10 compound (12-4) by the same production process as that  
described in literature (for example, Protective Groups  
in Organic Synthesis 2nd Edition (John Wiley & Sons,  
Inc.)) or the like.

5) Step 6

15 A compound (12-6) may be produced from the  
compound (12-5) by the same production process as  
described in the step 3, (4) in the production process  
1.

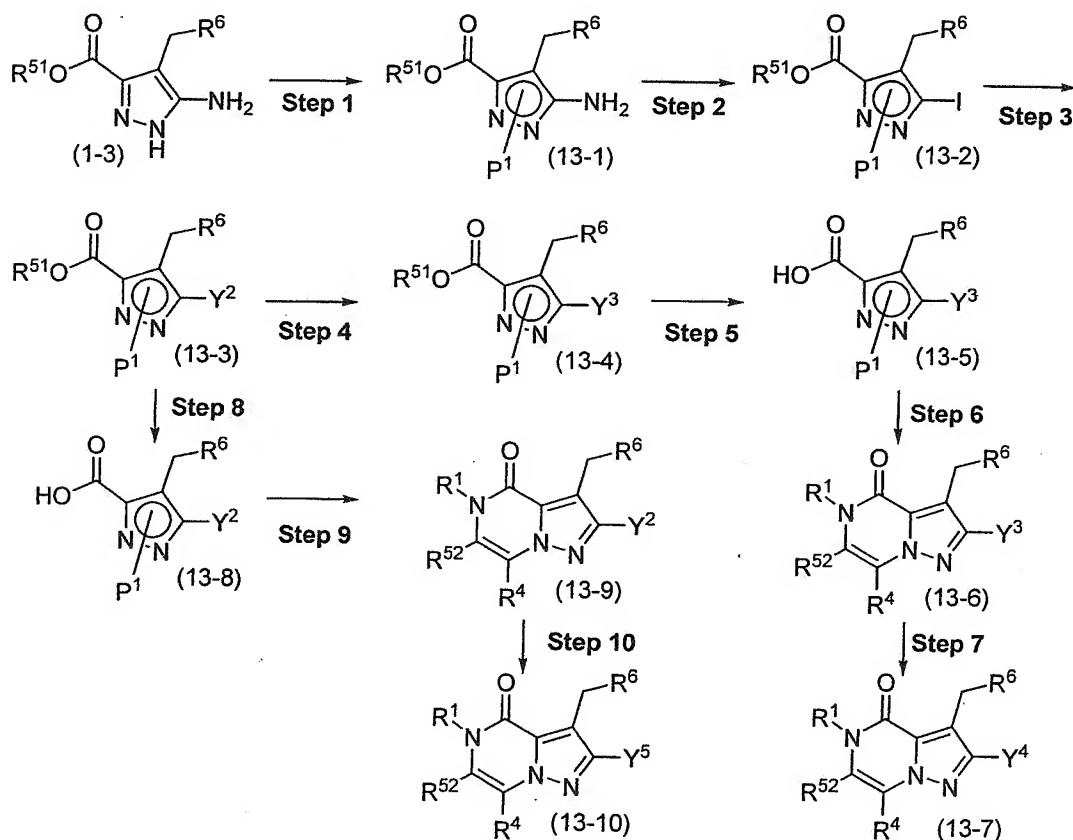
In this reaction, a compound in which the  
20 protective group for primary amino group or secondary  
amino group in  $Y^1$  has been removed is produced in some  
cases. The primary amino group or secondary amino  
group in Y may be protected again with a protective  
group (e.g. Boc or Cbz) by the same method as in the  
25 production process described in literature (for  
example, Protective Groups in Organic Synthesis 2nd  
Edition (John Wiley & Sons, Inc.)).

6) Step 7

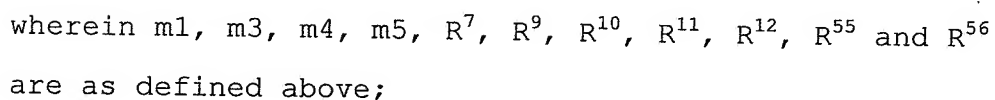
The compound (12-7) may be produced from the compound (12-6) by the same production process as described in the step 6 in the production process 1.

### Production Process 13

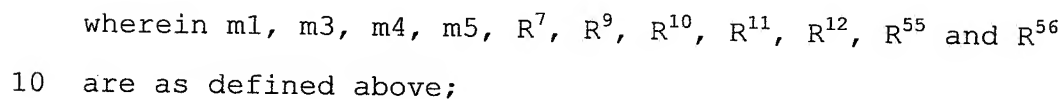
- 5 Each of compounds of the formula (13-7) and the formula (13-10) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:



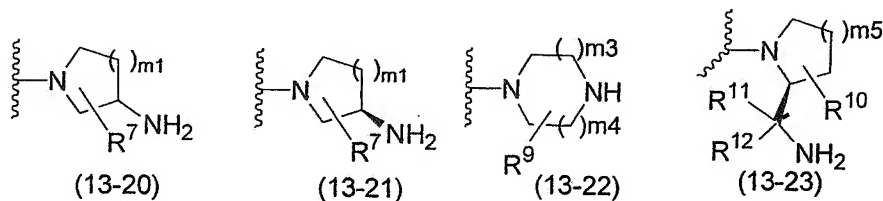
wherein  $R^1$ ,  $R^4$  and  $R^6$  are as defined in the item [1];  $R^{51}$   
 10 and  $R^{52}$  are as defined in the production process 1;  $P^1$   
 is as defined in the production process 6;  $Y^2$  represents



Y<sup>3</sup> represents the following formula (13-16), the following formula (13-17), the following formula (13-18) or the following formula (13-19):

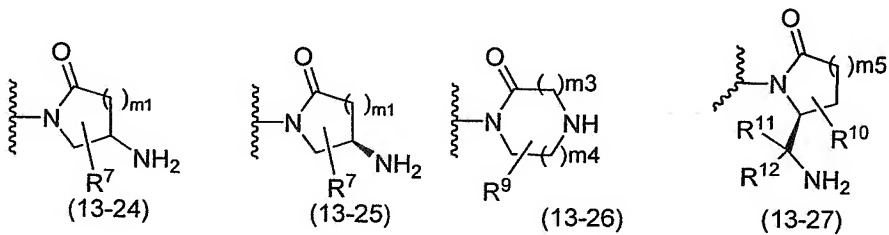


Y<sup>4</sup> represents the following formula (13-20), the following formula (13-21), the following formula (13-22) or the following formula (13-23):



wherein  $m_1$ ,  $m_3$ ,  $m_4$ ,  $m_5$ ,  $R^7$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$  and  $R^{12}$  are as defined above; and

$Y^5$  represents the following formula (13-24),  
the following formula (13-25), the following formula  
5 (13-26) or the following formula (13-27):



wherein  $m_1$ ,  $m_3$ ,  $m_4$ ,  $m_5$ ,  $R^7$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$  and  $R^{12}$  are as defined above.

#### 1) Step 1

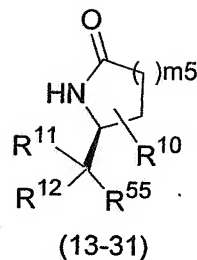
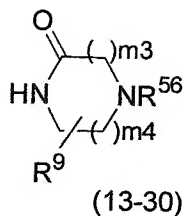
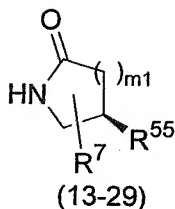
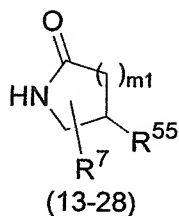
A compound (13-1) may be produced from a  
10 compound (1-3) by the same production process as described in the step 6 in the production process 6.

#### 2) Step 2

A compound (13-2) may be produced from the  
compound (13-1) by the same production process as  
15 described in the step 4 in the production process 1.

#### 3) Step 3

A compound (13-3) may be produced by reacting  
the compound (13-2) with a compound selected from a  
compound (13-28), a compound (13-29), a compound (13-  
20 30) and a compound (13-31) which are represented by the formulas:



wherein  $m_1$ ,  $m_3$ ,  $m_4$ ,  $m_5$ ,  $R^7$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{55}$  and  $R^{56}$  are as defined above, and the compound of the formula (13-29) is the same as the compound of the formula (23-4) described in the production process 23, in an inert solvent in the presence of potassium phosphate, ethylene glycol and copper iodide. The amount of the compound (13-28), compound (13-29), compound (13-30) or compound (13-31) used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (13-2). The amount of potassium phosphate used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (13-2). The amount of ethylene glycol used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (13-2). The amount of copper iodide used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (13-2). The inert solvent includes, for example, alcohol solvents (e.g. methanol, ethanol and 2-propanol). The reaction temperature may be chosen in the range of about 50°C to about 150°C. It is also possible to carry out the reaction in a closed reaction vessel such as an autoclave.

The compound (13-29) and the compound (13-30)

may be produced by the process described hereinafter as production process 23 and the process described hereinafter as production process 25, respectively. As the compound (13-28), a commercial reagent may be used, or the compound (13-28) may be produced by the process described in literature (for example, US5232929). As the compound (13-31), a commercial reagent may be used, or the compound (13-31) may be produced by the process described in literature (for example, Tetrahedron 51, 13309-20 (1995), Tetrahedron: Asymmetry 5, 887-94 (1994) and Tetrahedron: Asymmetry 4, 91-100 (1993)).

4) Step 4

A compound (13-4) may be produced by reacting the compound (13-3) with a reducing agent in an inert solvent. The reducing agent includes lithium aluminum hydride, borane complexes (e.g. borane-dimethyl sulfide complexes and borane-tetrahydrofuran complexes) and the like. The inert solvent includes tetrahydrofuran, 1,4-dioxane, mixed solvents thereof, and the like. The reaction temperature is chosen in the range of about -20°C to about 60°C. A preferable reaction temperature is chosen in the range of about -10°C to about 30°C.

5) Step 5

A compound (13-5) may be produced from the compound (13-4) by the same production process as described in the step 3, (2) in the production process 1.

6) Step 6

A compound (13-6) may be produced from the compound (13-5) by the same production process as described in the step 3, (3) and (4) in the production process 1.

5 7) Step 7

The compound (13-7) may be produced from the compound (13-6) by the same production process as described in the step 6 in the production process 1.

8) Step 8

10 A compound (13-8) may be produced from the compound (13-3) by the same production process as described in the step 3, (2) in the production process 1.

9) Step 9

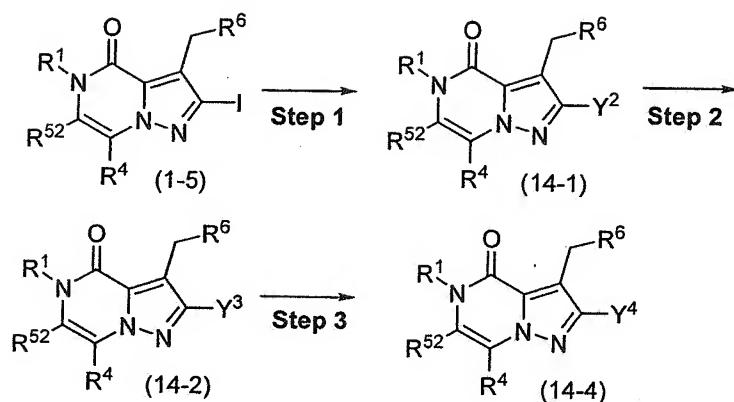
15 A compound (13-9) may be produced from the compound (13-8) by the same production process as described in the step 3, (3) and (4) in the production process 1.

10) Step 10

20 The compound (13-10) may be produced from the compound (13-9) by the same production process as described in the step 6 in the production process 1.

Production Process 14

A compound of the formula (14-4) as the  
25 compound of the formula (I), or a salt thereof is produced, for example, by the following process:



wherein  $R^1$ ,  $R^4$  and  $R^6$  are as defined in the item [1];  $R^{52}$  is as defined in the production process 1; and  $Y^2$ ,  $Y^3$  and  $Y^4$  are as defined in the production process 13.

#### 1) Step 1

5                   A compound (14-1) may be produced from a compound (1-5) by the same production process as described in the step 3 in the production process 13.

#### 2) Step 2

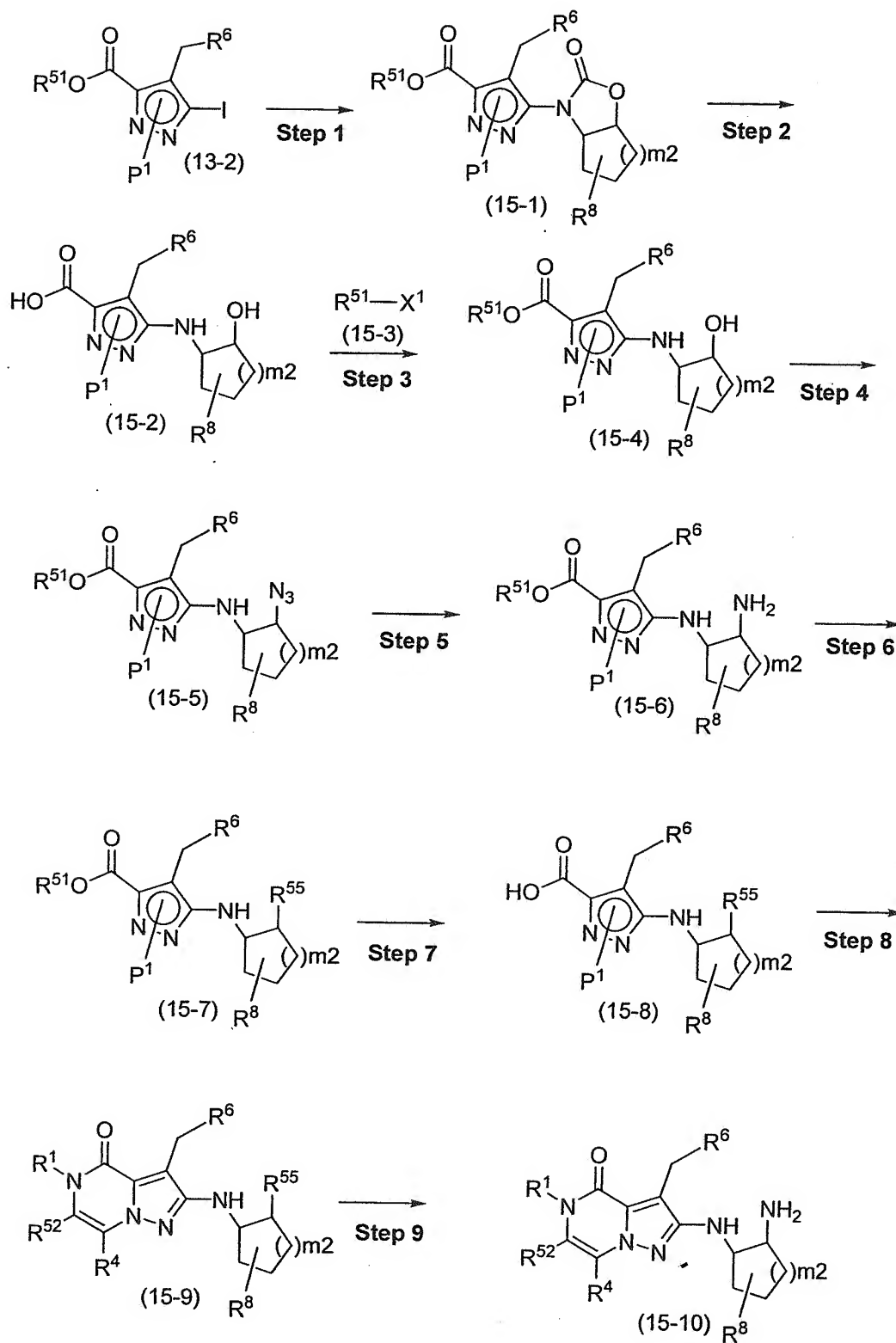
10                   A compound (14-2) may be produced from the compound (14-1) by the same production process as described in the step 4 in the production process 13.

#### 3) Step 3

15                   The compound (14-4) may be produced from the compound (14-2) by the same production process as described in the step 6 in the production process 1.

### Production Process 15

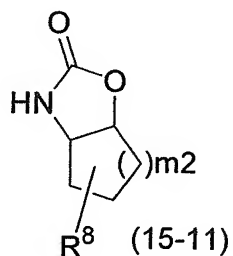
A compound of the formula (15-10) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:



wherein  $m_2$ ,  $R^1$ ,  $R^4$ ,  $R^6$  and  $R^8$  are as defined in the item [1];  $R^{51}$ ,  $R^{52}$  and  $R^{55}$  are as defined in the production process 1; and  $X^1$  and  $P^1$  are as defined in the production process 6.

5 1) Step 1

A compound (15-1) may be produced by reacting a compound (13-2) with a compound represented by the formula:



wherein  $R^8$  and  $m_2$  are as defined above, by the same method as in the production process described in literature (for example, J. Am. Chem. Soc. 124, 7421 (2002), Org. Lett. 5, 963 (2003) and Synlett 427 (2002)).

2) Step 2

15 A compound (15-2) may be produced from the compound (15-1) by the same production process as described in the step 3, (2) in the production process 1.

3) Step 3

20 A compound (15-4) may be produced by reacting the compound (15-2) with a compound (15-3) in an inert solvent in the presence of a base. The base includes sodium hydrogencarbonate, potassium hydrogencarbonate,

sodium carbonate, potassium carbonate, lithium carbonate and the like. The amount of the base used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (15-2). The amount of the  
5 compound (15-3) used is usually chosen in the range of 1 to 5 equivalents per equivalent of the compound (15-2). The inert solvent includes, for example, dimethylformamide, tetrahydrofuran and 1,4-dioxane. Mixed solvents thereof may also be used. The reaction  
10 temperature is chosen in the range of about  $-10^{\circ}\text{C}$  to about  $40^{\circ}\text{C}$ .

#### 4) Step 4

A compound (15-5) may be produced from the compound (15-4) by the same production process as  
15 described in literature (for example, Synthesis 130 (1990)).

#### 5) Step 5

A compound of the formula (15-6) may be produced by reacting the compound of the formula (15-5)  
20 in an inert solvent under a hydrogen atmosphere in the presence of a catalyst such as palladium-carbon. The inert solvent includes, for example, alcohol solvents such as ethanol, methanol, 2-propanol, etc.; ether solvents such as tetrahydrofuran, 1,4-dioxane, etc.;  
25 aprotic solvents such as dimethylformamide, etc.; organic acids such as acetic acid, propionic acid, etc.; and hydrocarbon solvents such as benzene, toluene, xylene, etc. Mixed solvents of these solvents

may also be used. The reaction temperature is chosen in the range of about 0°C to about 40°C.

6) Step 6

5 A compound (15-7) may be produced from the compound (15-6) by the same process as that described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)) or the like.

7) Step 7

10 A compound (15-8) may be produced from the compound (15-7) by the same production process as described in the step 3, (2) in the production process 1.

8) Step 8

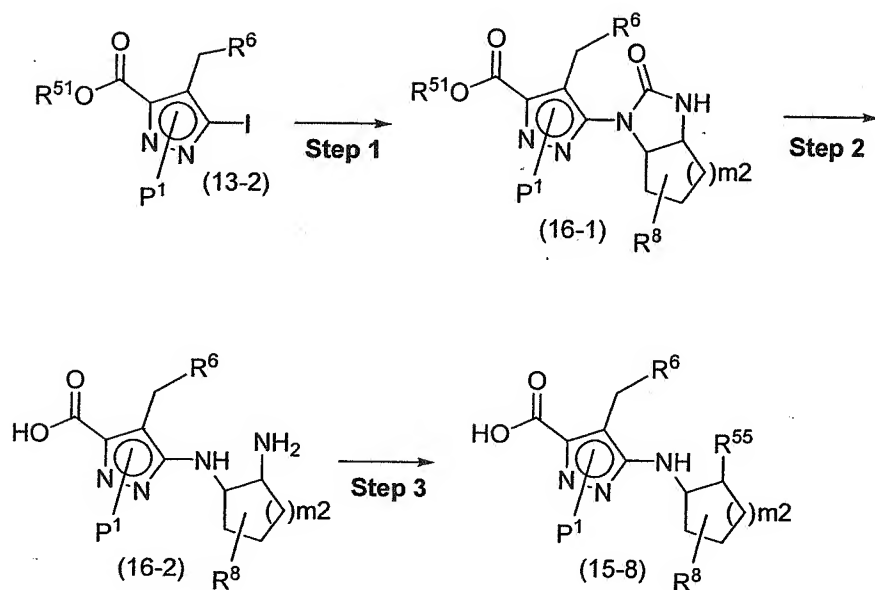
15 A compound (15-9) may be produced from the compound (15-8) by the same production process as described in the step 3, (3) to (4) in the production process 1.

9) Step 9

20 The compound (15-10) may be produced from the compound (15-9) by the same production process as described in the step 6 in the production process 1.

Production Process 16

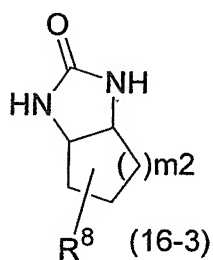
25 In the production process 15, the compound of the formula (15-8) or a salt thereof may be produced also by, for example, the following process:



wherein  $m_2$ ,  $R^6$  and  $R^8$  are as defined in the item [1];  $R^{51}$  and  $R^{55}$  are as defined in the production process 1; and  $P^1$  is as defined in the production process 6.

1) Step 1

5           A compound (16-1) may be produced by reacting a compound (13-2) with a compound (16-3) represented by the formula:



wherein  $R^8$  and  $m_2$  are as defined above, by the same method as in the production process described in  
 10 literature (for example, J. Am. Chem. Soc. 124, 7421 (2002)).

## 2) Step 2

A compound (16-2) may be produced from the compound (16-1) by the same production process as described in the step 3, (2) in the production process

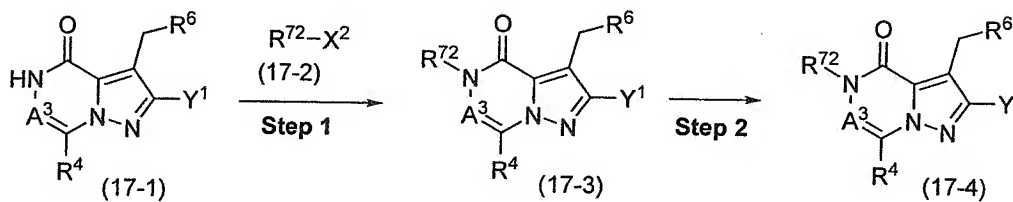
5 1.

## 3) Step 3

The compound (15-8) may be produced from the compound (16-2) by the same process as that described in literature (for example, Protective Groups in  
10 Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)) or the like.

## Production Process 17

A compound of the formula (17-4) as the  
15 compound of the formula (I), or a salt thereof is produced, for example, by the following process:



wherein R<sup>4</sup>, R<sup>6</sup> and Y are as defined in the item [1]; A<sup>3</sup> is as defined in the item [2]; Y<sup>1</sup> is as defined in the production process 1; the compound of the formula (17-  
20 1) is the compound (26-6) described in the production process 26 or the compound (27-3) described in the production process 27, or corresponds to the following compound when R<sup>1</sup> is a hydrogen atom: the compound (1-6)

described in the production process 1 or the production process 6, the compound (8-1), compound (8-4) or compound (8-6) described in the production process 8, the compound (9-3) described in the production process 9, the compound (10-4) or compound (10-6) described in the production process 10, the compound (12-6) described in the production process 12, the compound (13-6) or compound (13-9) described in the production process 13, the compound (14-2) described in the production process 14, the compound (15-9) described in the production process 15, the compound (28-10) described in the production process 28, the compound (29-7) described in the production process 29, or the compound (30-2) described in the production process 30;  $R^{72}$  is "an optionally substituted alkyl group" or "an optionally substituted cycloalkyl group", which is represented by  $R^1$  described in the item [1]; and  $X^2$  is a leaving group (for example, a bromine atom, a chlorine atom, methanesulfonyloxy, trifluoromethanesulfonyloxy or p-toluenesulfonyloxy).

1) Step 1

A compound (17-3) may be produced by reacting a compound (17-1) with a compound (17-2) in an inert solvent in the presence of a base. The base includes potassium tert-butoxide, sodium tert-butoxide, cesium carbonate, potassium carbonate, sodium carbonate, sodium phenoxide, potassium phenoxide, sodium hydride and the like. The amount of the base used is usually

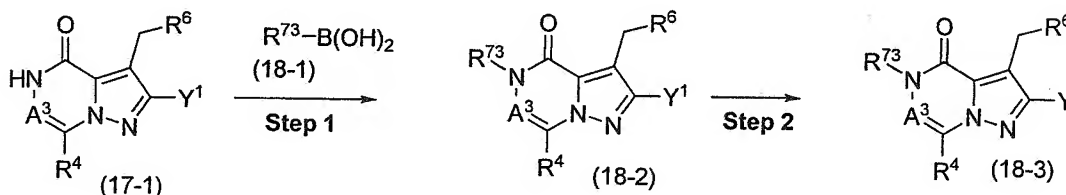
chosen in the range of 1 to 5 equivalents per equivalent of the compound (17-3). The inert solvent includes tetrahydrofuran, 1,4-dioxane, dimethylformamide, mixed solvents thereof, and the like. The reaction temperature may be chosen in the range of about 10°C to about 50°C.

## 2) Step 2

The compound (17-4) may be produced from the compound (17-3) by the same production process as described in the step 6 in the production process 1.

## Production Process 18

A compound of the formula (18-3) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:



wherein  $R^4$ ,  $R^6$  and  $Y$  are as defined in the item [1];  $A^3$  is as defined in the item [2];  $Y^1$  is as defined in the production process 1; the formula (17-1) is as defined above; and  $R^{73}$  is "an optionally substituted aryl group" or "an optionally substituted heteroaryl group", which is represented by  $R^1$  described in the item [1].

## 1) Step 1

A compound (18-2) may be produced from a

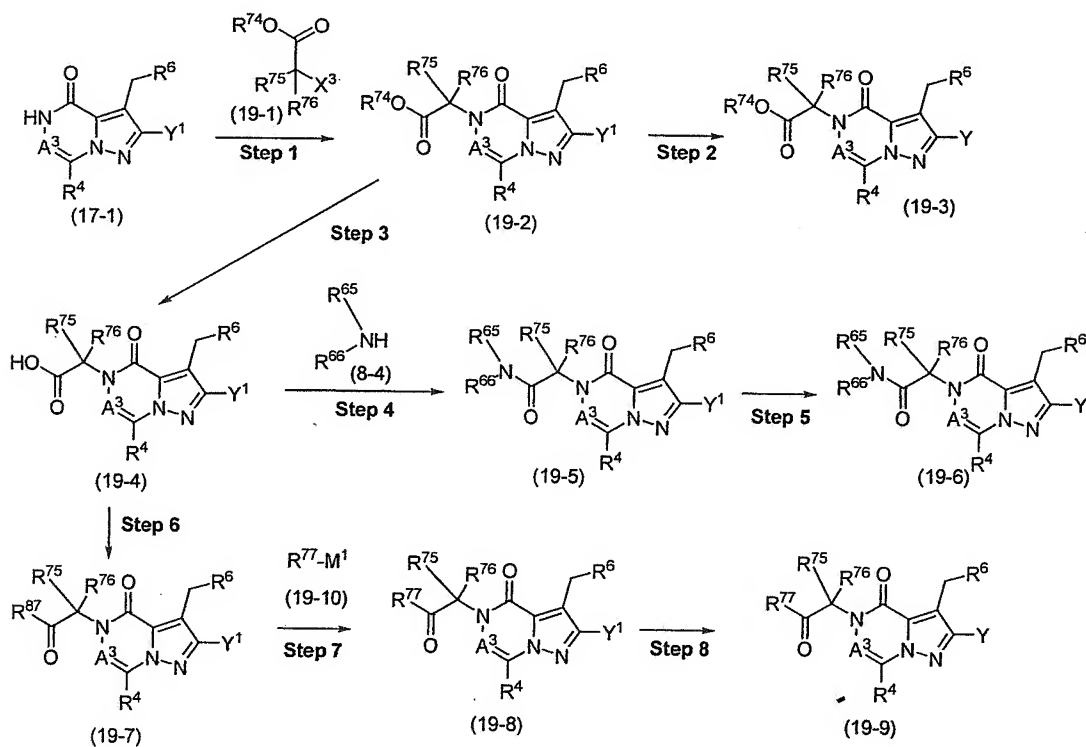
compound (17-1) by the same process as that described in literature (for example, Tetrahedron 55, 12757 (1999)) or the like.

## 2) Step 2

- 5           The compound (18-3) may be produced from the compound (18-2) by the same production process as described in the step 6 in the production process 1.

## Production Process 19

Each of compounds of the formula (19-3), the  
10 formula (19-6) and the formula (19-9) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:



wherein  $R^4$ ,  $R^6$  and  $Y$  are as defined in the item [1];  $A^3$  is as defined in the item [2];  $Y^1$  is as defined in the production process 1; the formula (17-1) is as defined above;  $R^{65}$  and  $R^{66}$  are as defined in the production  
5 process 8;  $R^{87}$  and  $M^1$  are as defined in the production process 9;  $X^3$  is a leaving group (for example, a bromine atom, a chlorine atom, methanesulfonyloxy, trifluoromethanesulfonyloxy or p-toluenesulfonyloxy);  $R^{74}$  is an alkyl group;  $R^{75}$  and  $R^{76}$  are independently a  
10 hydrogen atom, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy or isopropoxy, or  $R^{75}$  and  $R^{76}$ , when taken together with the adjacent carbon atom, may form cyclopropyl, cyclobutyl or cyclopentyl; and  $R^{77}$  is an optionally substituted alkyl group, an optionally  
15 substituted aryl group or an optionally substituted heteroaryl group.

1) Step 1

A compound (19-2) may be produced from a compound (17-1) by the same production process as  
20 described in the step 1 in the production process 17.

2) Step 2

The compound (19-3) may be produced from the compound (19-2) by the same production process as described in the step 6 in the production process 1.

25 3) Step 3

A compound (19-4) may be produced from the compound (19-2) by the same production process as described in the step 3, (2) in the production process

1.

## 4) Step 4

A compound (19-5) may be produced from the compound (19-4) by the same production process as

5 described in the step 2 in the production process 8.

## 5) Step 5

The compound (19-6) may be produced from the compound (19-5) by the same production process as described in the step 6 in the production process 1.

## 10 6) Step 6 to Step 7

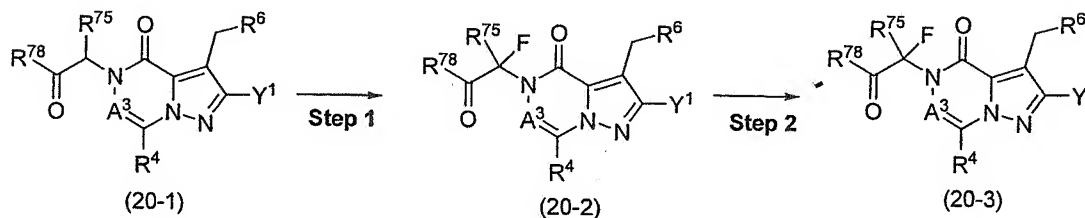
A compound (19-8) may be produced from the compound (19-4) by the same production process as described in the step 1 to step 2 in the production process 9.

## 15 7) Step 8

The compound (19-9) may be produced from the compound (19-8) by the same production process as described in the step 6 in the production process 1.

## Production Process 20

20 A compound of the formula (20-3) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:



wherein  $R^4$ ,  $R^6$  and  $Y$  are as defined in the item [1];  $A^3$  is as defined in the item [2];  $Y^1$  is as defined in the production process 1; the compound of the formula (20-1) corresponds to the compound (19-2), compound (19-5) or compound (19-8) described in the production process 19 when  $R^{76}$  is a hydrogen atom;  $R^{78}$  corresponds to  $R^{74}O$ ,  $R^{65}R^{66}N$  or  $R^{77}$  in the production process 19; and  $R^{65}$ ,  $R^{66}$ ,  $R^{74}$  and  $R^{77}$  are as defined above.

1) Step 1

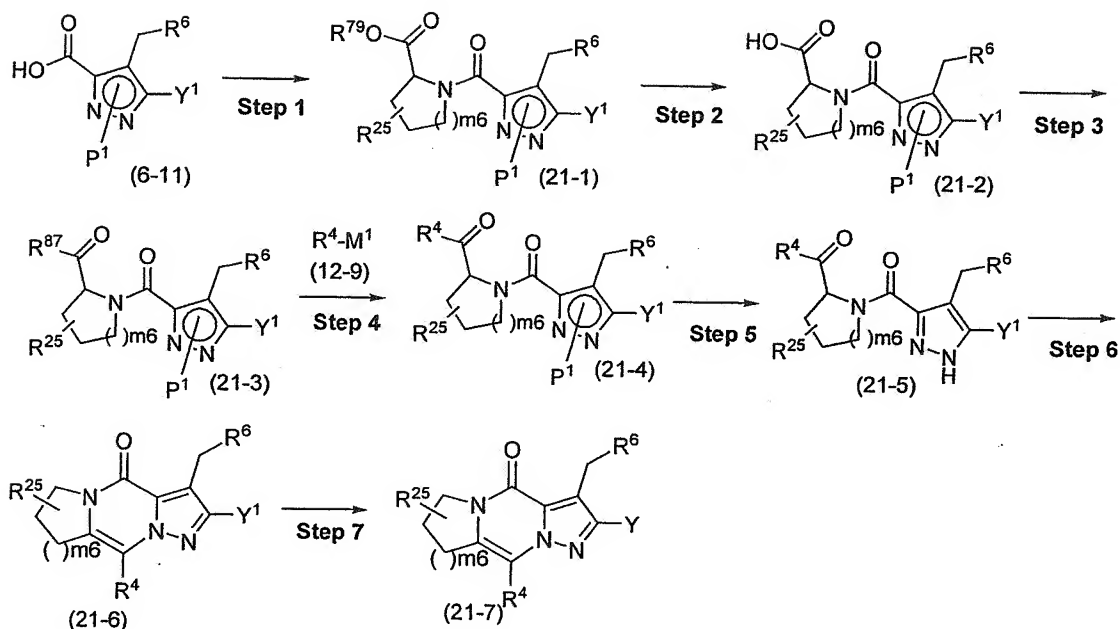
10           A compound (20-2) may be produced from a compound (20-1) by the same production process as described in literature (for example, Angew. Chem. 108, 1082 (1996), Bioorg. Med. Chem. Lett. 8, 3275 (1998) and Tetrahedron Lett. 32, 1779 (1991)).

15   2) Step 2

          The compound (20-3) may be produced from the compound (20-2) by the same production process as described in the step 6 in the production process 1.

Production Process 21

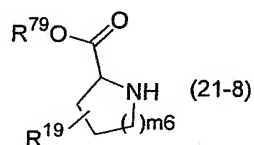
20           A compound of the formula (21-7) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:



wherein  $R^4$ ,  $R^6$  and  $Y$  are as defined in the item [1];  $R^{79}$  is an alkyl group;  $Y^1$  is as defined in the production process 1;  $P^1$  is as defined in the production process 6;  $R^{87}$  and  $M^1$  are as defined in the production process 9; 5 and  $m6$  and  $R^{25}$  are as defined above.

#### 1) Step 1

A compound (21-1) may be produced by reacting a compound (6-11) with a compound (21-8) represented by the formula:



10 wherein  $m6$ ,  $R^{25}$  and  $R^{79}$  are as defined above, by the same method as in the production process described in the step 3, (3) in the production process 1.

## 2) Step 2

A compound (21-2) may be produced from the compound (21-1) by the same production process as described in the step 3, (2) in the production process

5 1.

## 3) Step 3 to Step 4

A compound (21-4) may be produced from the compound (21-2) by the same production process as described in the step 1 to step 2 in the production

10 process 9.

## 4) Step 5

A compound (21-5) may be produced from the compound (21-4) by the same process as that described in literature (for example, Protective Groups in

15 Organic Synthesis 2nd Edition (John Wiley &amp; Sons, Inc.)) or the like.

## 5) Step 6

A compound (21-6) may be produced from the compound (21-5) by the same production process as

20 described in the step 3, (4) in the production process 1.

## 6) Step 7

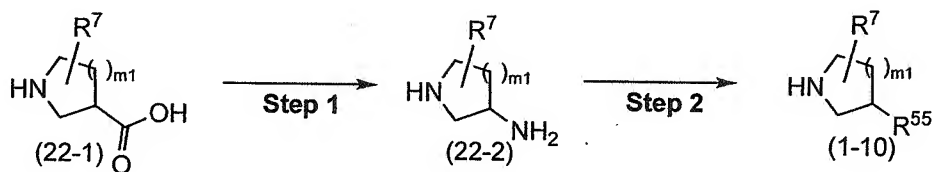
The compound (21-7) may be produced from the compound (21-6) by the same production process as

25 described in the step 6 in the production process 1.

## Production Process 22

The compound (1-10) described in the

production process 1 may be produced, for example, by the following process:



wherein R<sup>7</sup> and m1 are as defined in the item [1], and R<sup>55</sup> is as defined in the production process 1.

5 1) Step 1

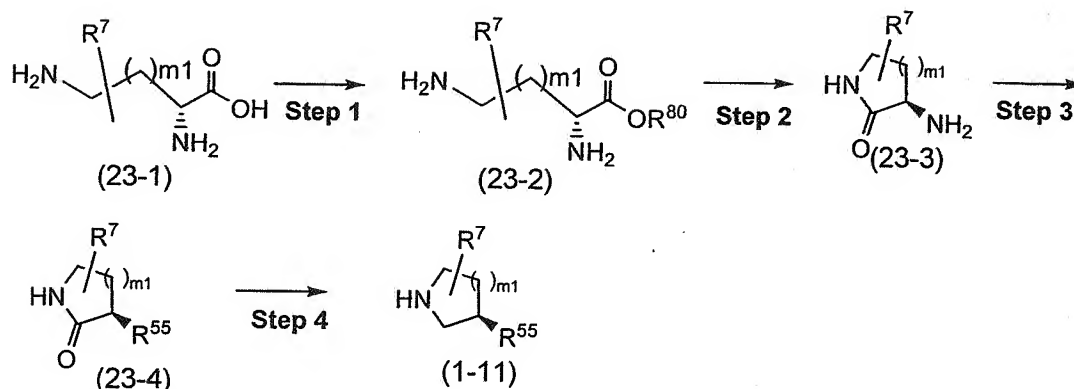
A compound (22-2) may be produced from a compound (22-1) by the same production process as described in literature (for example, J. Org. Chem. 58, 879 (1993)).

10 2) Step 2

The compound (1-10) may be produced from the compound (22-2) by the same process as that described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)) or the like.

Production Process 23

Each of the compound (1-11) described in the production process 1 and the compound described in the production process 13 may be produced, for example, by the following process:



wherein  $\text{R}^7$  and  $m_1$  are as defined in the item [1];  $\text{R}^{55}$  is as defined in the production process 1; and  $\text{R}^{80}$  is an alkyl group.

#### 1) Step 1

5 A compound (23-2) may be produced by reacting a compound (23-1) with thionyl chloride in an alcohol solvent. The alcohol solvent includes methanol, ethanol and the like. The amount of thionyl chloride used is usually chosen in the range of 2 to 10

10 equivalents per equivalent of the compound (23-1). The reaction temperature may be chosen in the range of about  $-90^\circ\text{C}$  to about  $30^\circ\text{C}$ .

#### 2) Step 2

A compound (23-3) may be produced by reacting

15 the compound (23-2) with a base in water solvent. The base includes sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate and the like. The reaction temperature may be chosen in the range of about  $30^\circ\text{C}$  to about  $100^\circ\text{C}$ .

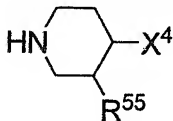
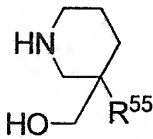
#### 20 3) Step 3

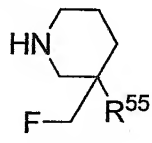
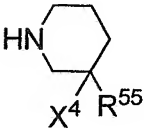
A compound (23-4) may be produced from the compound (23-3) by the same process as that described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)) or the like.

4) Step 4

The compound (1-11) may be produced by reacting the compound (23-4) with a reducing agent in an inert solvent. The reducing agent includes lithium aluminum hydride, borane complexes (e.g. borane-dimethyl sulfide complexes and borane-tetrahydrofuran complexes) and the like. The inert solvent includes tetrahydrofuran, 1,4-dioxane, mixed solvents thereof, and the like. The reaction temperature is chosen in the range of about  $-20^{\circ}\text{C}$  to about  $60^{\circ}\text{C}$ .

Examples of synthesis of compounds (1-10a) to (1-10j) as specific examples of the compound (1-10) are given below. The compounds (1-10a) to (1-10j) include pharmaceutically acceptable salts thereof.

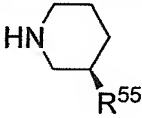
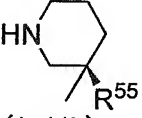
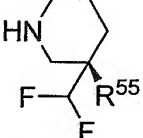
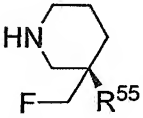
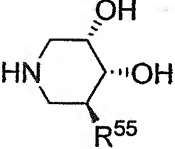
Compound	Production process
	WO 02/48138 J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
(1-10a): $\text{X}^4 = \text{CH}_3$	
(1-10b): $\text{X}^4 = \text{CH}_2\text{CH}_3$	
(1-10c): $\text{X}^4 = \text{CH}_2\text{CH}_2\text{OH}$	
(1-10d): $\text{X}^4 = \text{CH}_2\text{CH}_2\text{F}$	
(1-10e): $\text{X}^4 = \text{H}$	
	J. Org. Chem. 44, 2732 (1979) J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
(1-10f)	

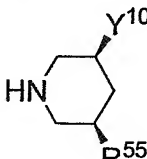
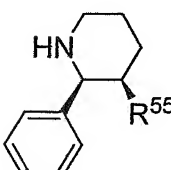
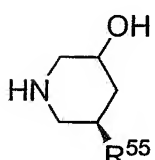
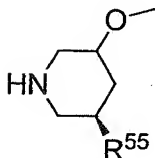
Compound	Production process
 (1-10g)	Compound (1-10f) is used as a starting material and the process described in, for example, J. Org. Chem. 44, 3872 (1979), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.) is adopted.
 (1-10h): $X^4 = CH_3$ (1-10i): $X^4 = CH_2CH_3$ (1-10j): $X^4 = CH_2CH_2CH_3$	Arch. Pharm. 322, 499 (1989) J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)

In the above formulas,  $R^{55}$  is as defined in the production process 1.

As hydrochloride of the compound (1-10e), a commercial one may also be used. It is also possible to synthesize the compound (1-10) from a substituted DL-ornithine by a well-known process. A specific  
 5 example of the process is the process described in literature (for example, R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., 1989).

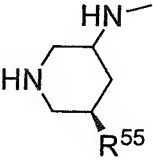
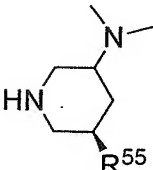
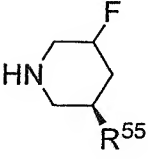
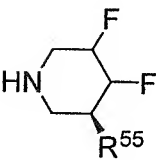
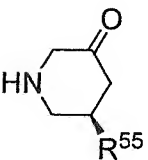
Examples of synthesis of compounds (1-11a) to (1-11j) as specific examples of the compound (1-11) are  
 10 given below. The compounds (1-11a) to (1-11j) include pharmaceutically acceptable salts thereof.

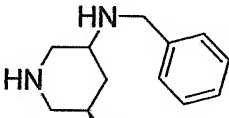
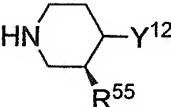
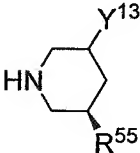
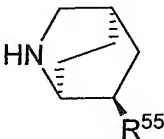
Compound	Production process
 (1-11a)	WO 01/27082 J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-11b)	Int. J. Peptide Protein Res. 40, 119 (1992) WO 01/27082 J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-11c)	US 4413141 WO 01/27082 J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-11d)	Tetrahedron: Asymmetry 8, 327 (1997) WO 01/27082 J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-11e)	Tetrahedron: Asymmetry 11, 567 (2000) J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)

Compound	Production process
 (1-11f)	Chem. Eur. J. 6, 2830 (2000) WO 00/26332 J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-11g)	Japanese Patent Application Kohyo No. 2002-525325 J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-11h)	Bull. Chem. Soc. Jpn. 53, 2605 (1980) J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)
 (1-11i)	Compound (1-11h) is used as a starting material and the process described in, for example, J. Am. Chem. Soc. 80, 2584 (1958), J. Chem. Soc. PT1 499 (1972), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.) is adopted.

In the above formulas, R<sup>55</sup> is as defined in the production process 1, and Y<sup>10</sup> is NH<sub>2</sub>, NHBoc or NHCbz.

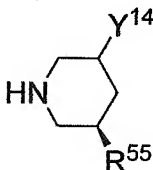
Examples of synthesis of compounds (1-11j) to (1-11v) as specific examples of the compound (1-11) are given below. The compounds (1-11j) to (1-11v) include pharmaceutically acceptable salts thereof.

Compound	Production process
 <p data-bbox="358 562 451 590">(1-11j)</p>	<p>Compound (1-11f in which R<sup>55</sup> is NH<sub>2</sub>) is used as a starting material and the process described in, for example,</p> <p>J. Chem. Soc. Chem. Commun. 611 (1981),  J. Chem. Soc., Perkin Trans. 1, 2233 (1999)  Protective Groups in Organic Synthesis  2nd Edition (John Wiley &amp; Sons, Inc.)  is adopted.</p>
 <p data-bbox="354 919 451 947">(1-11k)</p>	<p>Compound (1-11f in which R<sup>55</sup> is NH<sub>2</sub>) is used as a starting material and the process described in, for example,</p> <p>J. Chem. Soc. Chem. Commun. 611 (1981),  J. Chem. Soc., Perkin Trans. 1, 2233 (1999)  Protective Groups in Organic Synthesis  2nd Edition (John Wiley &amp; Sons, Inc.)  is adopted.</p>
 <p data-bbox="358 1220 451 1247">(1-11l)</p>	<p>Compound (1-11h) is used as a starting material and the process described in, for example,</p> <p>J. Org. Chem. 44, 3872 (1979),  J. Chem. Soc., Perkin Trans. 1, 2233 (1999)  Protective Groups in Organic Synthesis  2nd Edition (John Wiley &amp; Sons, Inc.)  is adopted.</p>
 <p data-bbox="329 1493 435 1520">(1-11m)</p>	<p>Compound (1-11e) is used as a starting material and the process described in, for example,</p> <p>J. Org. Chem. 44, 3872 (1979),  J. Chem. Soc., Perkin Trans. 1, 2233 (1999)  Protective Groups in Organic Synthesis  2nd Edition (John Wiley &amp; Sons, Inc.)  is adopted.</p>
 <p data-bbox="334 1787 435 1814">(1-11n)</p>	<p>Compound (1-11h) is used as a starting material and the process described in, for example,</p> <p>Bull. Chem. Soc. Jpn. 64, 2857 (1991),  J. Chem. Soc., Perkin Trans. 1, 2233 (1999)  Protective Groups in Organic Synthesis  2nd Edition (John Wiley &amp; Sons, Inc.)  is adopted.</p>

Compound	Production process
 <p>(1-11o)</p>	<p>Compound (1-11f i which <math>R^{55}</math> is <math>NH_2</math>) is used as a starting material and the process described in, for example, Tetrahedron Lett. 40, 5609(1999), J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley &amp; Sons, Inc.) is adopted.</p>
 <p>(1-11p): <math>Y^{12} = (R)-C_6H_5</math>  (1-11q): <math>Y^{12} = (S)-C_6H_5</math></p>	<p>J. Med. Chem. 35, 833 (1992), R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., 1989, J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley &amp; Sons, Inc.)</p>
 <p>(1-11r): <math>Y^{13} = NHS(O)_2CH_3</math>  (1-11s): <math>Y^{13} = NHC(O)CH_3</math>  (1-11t): <math>Y^{13} = NHC(O)C_6H_5</math>  (1-11u): <math>Y^{13} = N(CH_3)C(O)CH_3</math></p>	<p>Compound (1-11f in which <math>R^{55}</math> is <math>NH_2</math>) is used as a starting material and the process described in, for example, R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., 1989, J. Chem. Soc., Perkin Trans. 1, 2233 (1999) Protective Groups in Organic Synthesis 2nd Edition (John Wiley &amp; Sons, Inc.) is adopted.</p>
 <p>(1-11v)</p>	<p>WO 02/068420  J. Chem. Soc., Perkin Trans. 1, 2233 (1999)  Protective Groups in Organic Synthesis 2nd Edition (John Wiley &amp; Sons, Inc.)</p>

In the above formula,  $R^{55}$  is as defined in the production process 1.

Examples of synthesis of compounds (1-11w) to (1-11dd) as specific examples of the compound (1-11) are given below. The compounds (1-11w) to (1-11dd) include pharmaceutically acceptable salts thereof.

Compound	Production Process
	<p>Compound (1-11n) is used as a starting material and the process described in, for example, R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., 1989</p> <p>J. Org. Chem. 66, 3593 (2001),  J. Prakt. Chem. 342, 421 (2000),  Tetrahedron Lett. 36, 5611 (1994),  J. Org. Chem. 53, 5143 (1988),  Bioorg. Med. Chem. Lett. 11, 1281 (2001),  J. Chem. Soc., Perkin Trans. 1, 2233 (1999)  Protective Groups in Organic Synthesis  2nd Edition (John Wiley &amp; Sons, Inc.)  is adopted.</p>

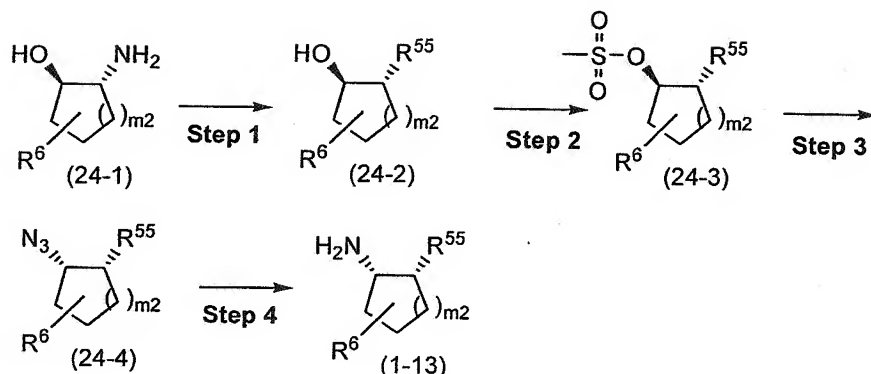
- (1-11w):  $Y^{14} = 2\text{-CH}_3\text{-C}_6\text{H}_5$   
(1-11x):  $Y^{14} = 3\text{-CH}_3\text{-C}_6\text{H}_5$   
(1-11y):  $Y^{14} = 4\text{-CH}_3\text{-C}_6\text{H}_5$   
(1-11z):  $Y^{14} = 2\text{-CH}_3\text{O-C}_6\text{H}_5$   
(1-11aa):  $Y^{14} = 3\text{-CH}_3\text{O-C}_6\text{H}_5$   
(1-11bb):  $Y^{14} = 4\text{-CH}_3\text{O-C}_6\text{H}_5$   
(1-11cc):  $Y^{14} = \text{C}_6\text{H}_5$   
(1-11dd):  $Y^{14} = \text{CH}_2\text{C}_6\text{H}_5$

In the above formula,  $R^{55}$  is as defined in the production process 1.

The compound (1-11) may be synthesized from a substituted D-ornithine by a well-known process. A specific example of the process is the process described in literature (for example, R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., 1989).

#### Production Process 24

The compound (1-13) described in the production process 1 may be produced, for example, by the following process:



wherein R<sup>6</sup> and m<sub>2</sub> are as defined in the item [1], and R<sup>55</sup> is as defined in the production process 1.

1) Step 1

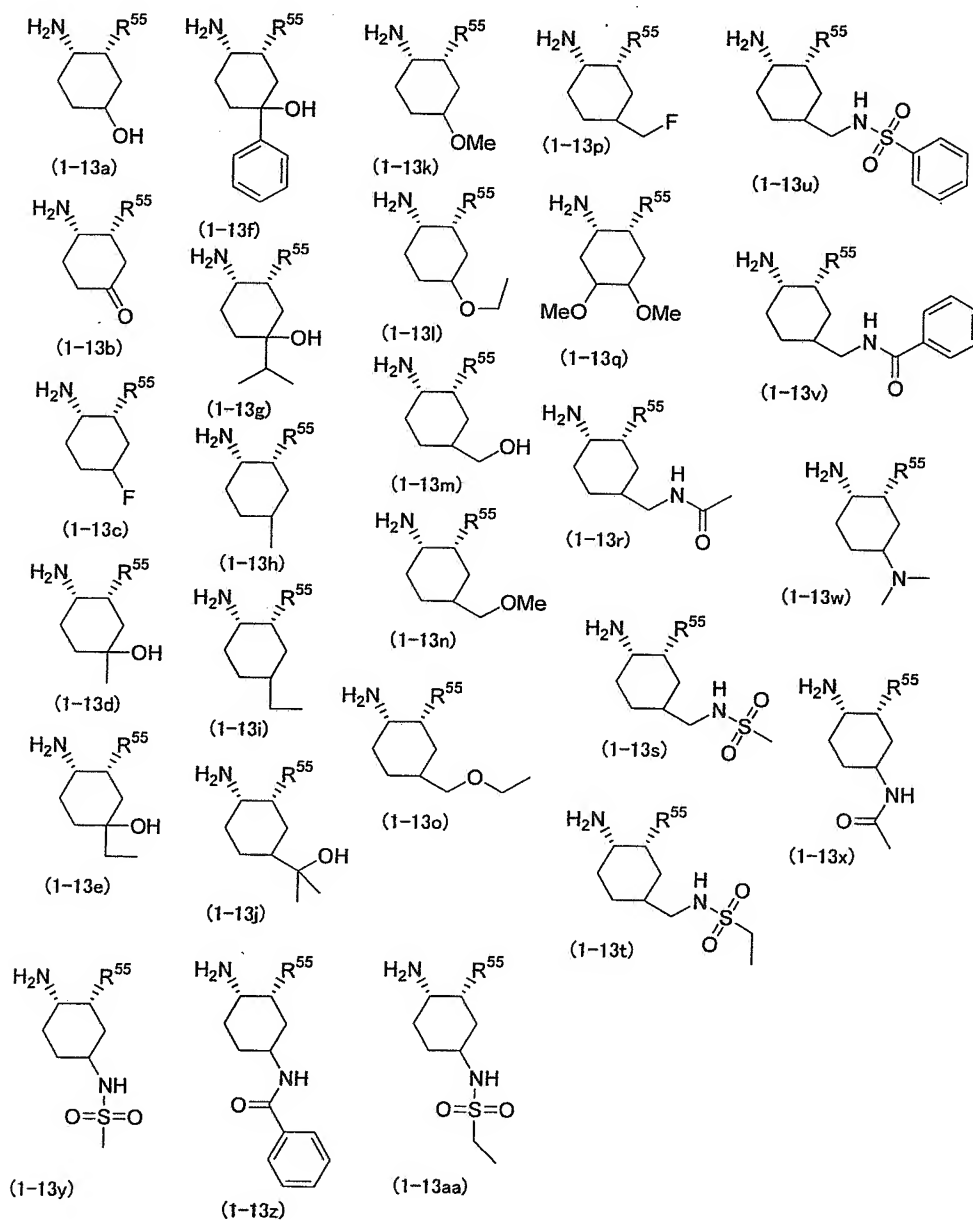
A compound (24-2) may be produced from a compound (24-1) by the same process as described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)) or the like. The compound (24-1) may be produced by the same production process as described in literature (for example, J. Org. Chem. 50, 4154 (1985)).

2) Step 2 to Step 4

The compound (1-13) may be produced from the compound (24-2) by the same process as described in literature (for example, R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., 1989).

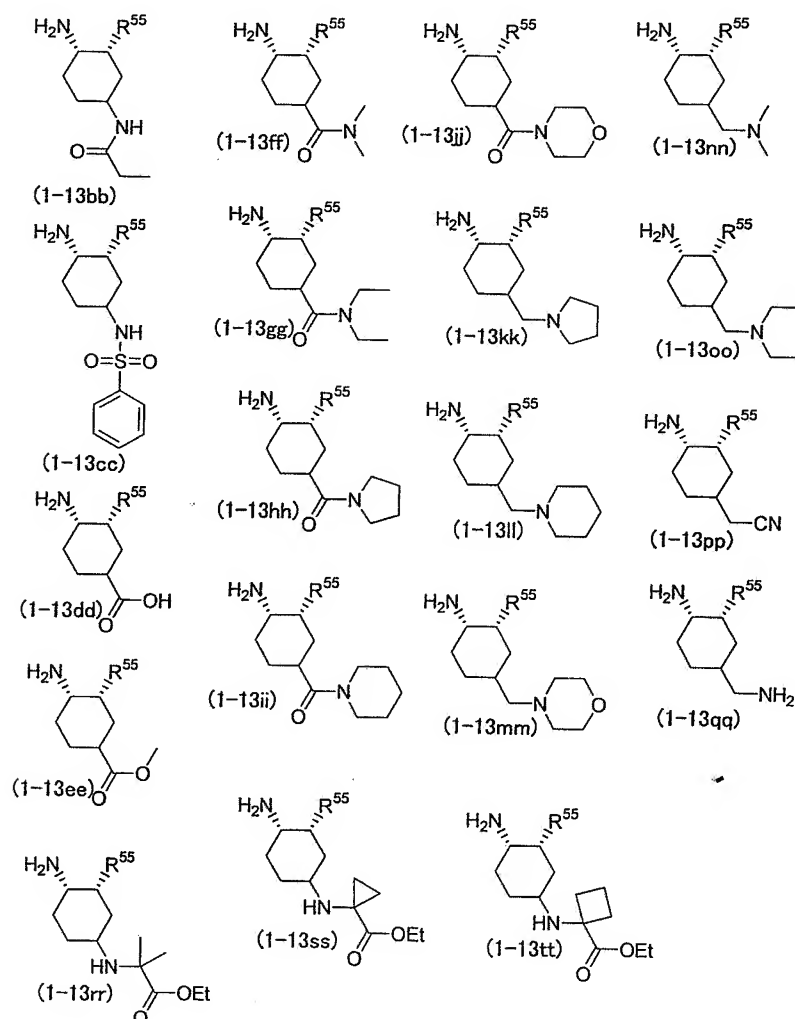
Examples of synthesis of compounds (1-13a) to (1-13aa) as specific examples of the compound (1-13) are given below. The compounds (1-13a) to (1-13aa) include pharmaceutically acceptable salts thereof. The

compounds (1-13a) to (1-13aa) may be produced according to the processes described in literature (for example, WO01/74774, and R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., 1989).



In the above formulas,  $R^{55}$  is as defined in the production process 1.

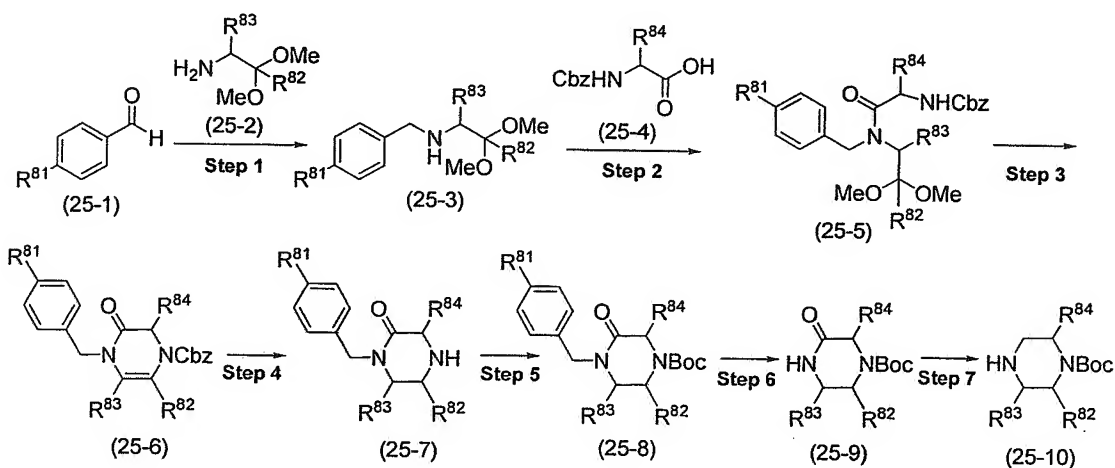
Examples of synthesis of compounds (1-13bb) to (1-13tt) as specific examples of the compound (1-13) are given below. The compounds (1-13bb) to (1-13tt) include pharmaceutically acceptable salts thereof. The compounds (1-13bb) to (1-13tt) may be produced according to the processes described in literature (for example, W001/74774, R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., 1989, and Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)).



In the above formulas,  $R^{55}$  is as defined in the production process 1.

### Production Process 25

Each of a compound (25-9) as a specific example of the compound (1-14) described in the production process 1 and a compound (25-8) as a specific example of the compound (13-10) described in the production process 13 may be produced according to, for example, the following process:



wherein  $R^{82}$ ,  $R^{83}$  and  $R^{84}$  are independently "a hydrogen atom", "an optionally substituted alkyl group", "an optionally substituted aryl group" or "an optionally substituted aralkyl group", and  $R^{81}$  is a hydrogen atom or methoxy.

#### 1) Step 1

A compound (25-3) may be produced by carrying out reductive amination of a compound (25-1) with a compound (25-2) by the same method as described in

literature (for example, R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., 1989).

2) Steps 2 to 4

A compound (25-7) may be produced from the  
5 compound (25-3) by the same production process as described in literature (W001/07436 and the like).

3) Step 5

The compound (25-8) may be produced from the compound (25-7) by the same production process as  
10 described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)).

4) Step 6

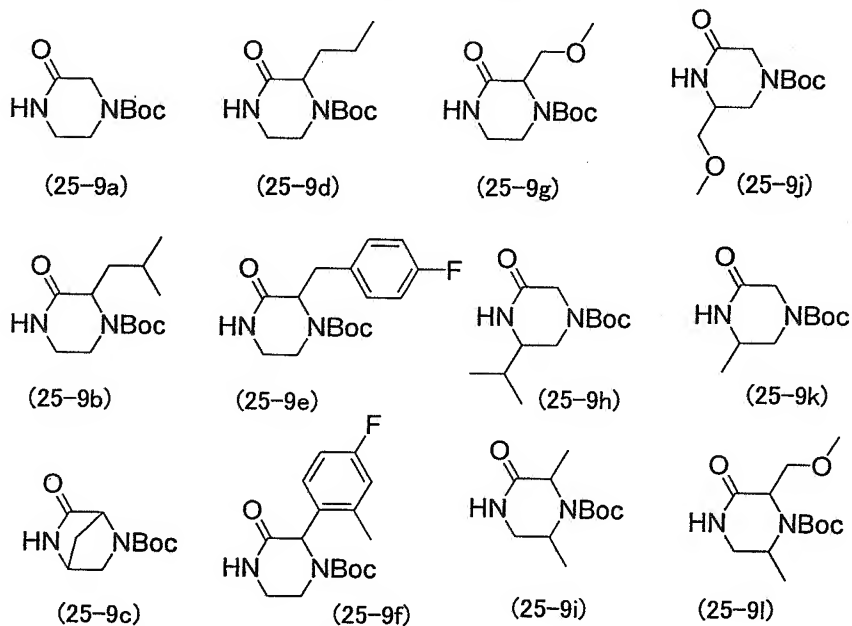
The compound (25-9) may be produced from the  
15 compound (25-8) by the same production process as described in literature (for example, J. Chem. Soc. Perkin Trans. I 3281 (2001), Heterocycles 38, 17 (1994), Tetrahedron Lett. 34, 6673 (1993), J. Org. Chem. 60, 4602 (1995) and J. Med. Chem. 38, 2866  
20 (1995)).

5) Step 7

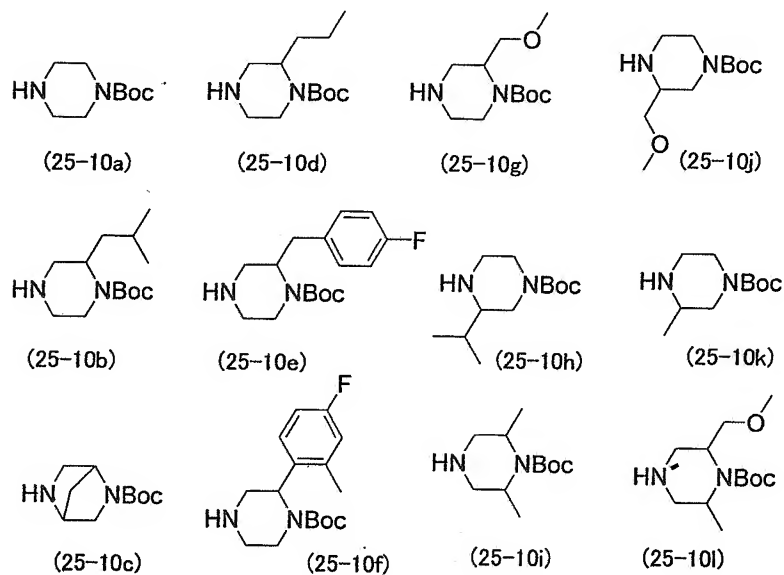
A compound (25-10) may be produced from the compound (25-9) by the same process as that described in literature (for example, R.C. Ralock, "Comprehensive  
25 Organic transformation", VCH publisher Inc., 1989) or the like.

Examples of synthesis of compounds (25-9a) to (25-9l) as specific examples of the compound (25-9) are

given below. The compounds (25-9a) to (25-9l) include pharmaceutically acceptable salts thereof.

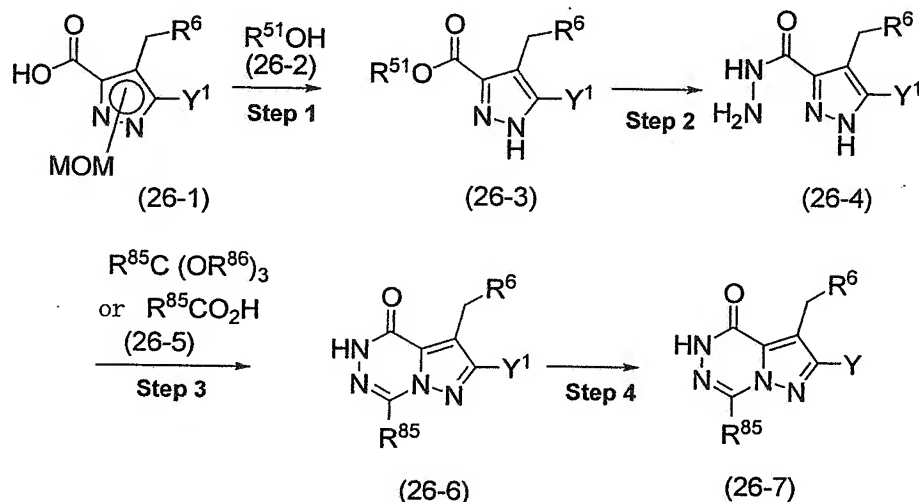


Examples of synthesis of compounds (25-10a) to (25-10l) as specific examples of the compound (25-10) are given below. The compounds (25-10a) to (25-10l) include pharmaceutically acceptable salts thereof.



## Production Process 26

A compound of the formula (26-7) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:



- 5 wherein R<sup>6</sup> and Y are as defined in the item [1]; R<sup>51</sup> and Y<sup>1</sup> are as defined in the production process 1; the compound of the formula (26-1) corresponds to the compound of the formula (6-11) described in the production process 6 when P<sup>1</sup> is a MOM group; R<sup>85</sup> is "a
- 10 hydrogen atom", "an optionally substituted alkyl group", "an optionally substituted cycloalkyl group", "an optionally substituted alkoxy group", "an optionally substituted alkoxycarbonyl group", "an optionally substituted alkylamino group", "an
- 15 optionally substituted aryl group", "an optionally substituted aralkyl group", "an optionally substituted heteroaryl group" or "an optionally substituted heteroarylalkyl group"; and R<sup>86</sup> is an alkyl group.

## 1) Step 1

A compound (26-3) may be produced by reacting a compound (26-1) with a compound (26-2) in an alcohol solvent in the presence of an acid. The acid includes  
5 hydrochloric acid, phosphoric acid, sulfuric acid and the like. A preferable example thereof is hydrochloric acid. The acid may be used as a solvent. The amount of the acid used is usually chosen in the range of a catalytic amount to a large excess over the alcohol  
10 solvent. The alcohol solvent includes, for example, methanol, ethanol and 2-propanol. The reaction temperature is chosen in the range of about 50°C to about 150°C, and the reaction is carried out with refluxing or in a sealed tube. In the reaction, a  
15 compound in which the protective group for primary amino group or secondary amino group in Y<sup>1</sup> has been removed is produced in some cases. The primary amino group or secondary amino group in Y may be protected again with a protective group (e.g. Boc or Cbz) by the  
20 same method as in the production process described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)).

## 2) Step 2

A compound (26-4) is produced by reacting the  
25 compound (26-3) with hydrazine monohydrate in the presence or absence of an inert solvent. When the inert solvent is present, the amount of hydrazine monohydrate used is usually chosen in the range of 1

equivalent to large excess equivalents per equivalent of the compound (26-3). When the inert solvent is absent, hydrazine monohydrate may be used as a solvent. The inert solvent includes, for example, alcohol solvents (e.g. methanol, ethanol and 2-propanol) and dimethylformamide. The reaction temperature is chosen in the range of about 50°C to about 170°C, and the reaction is usually carried out with refluxing.

3) Step 3

10           When the compound (26-5) is  $R^{85}C(OR^{86})_3$ , a compound (26-6) may be produced by reacting the compound (26-4) with the compound (26-5) in an inert solvent in the presence of an acid. The amount of the compound (26-5) used is usually chosen in the range of  
15 1 equivalent to large excess equivalents per equivalent of the compound (26-4). The acid includes inorganic acids such as hydrochloric acid, sulfuric acid, etc.; and organic acids such as trifluoroacetic acid, acetic acid, etc. The inert solvent includes, for example,  
20 alcohol solvents (e.g. methanol, ethanol and 2-propanol) and dimethylformamide. The acid may be used as a solvent. The reaction temperature is chosen in the range of about 50°C to about 150°C. When the compound (26-5) is  $R^{85}CO_2H$ , a compound (26-6) may be  
25 produced by reacting the compound (26-4) with the compound (26-5) in the presence of an acid. The amount of the compound (26-5) used is usually chosen in the range of 1 equivalent to large excess equivalents per

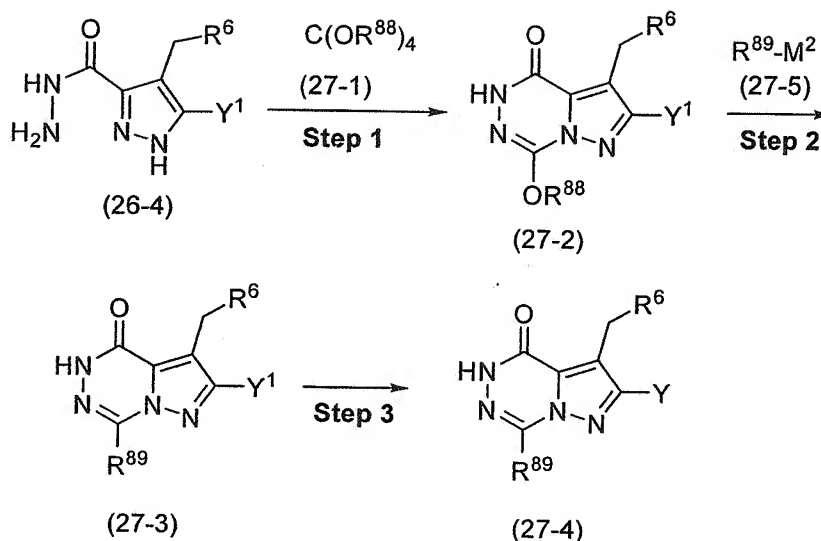
equivalent of the compound (26-4). The acid includes inorganic acids such as hydrochloric acid, sulfuric acid, polyphosphoric acid, etc. The acid may be used as a solvent. The reaction temperature is chosen in the range of about 50°C to about 200°C. In the reaction, a compound in which the protective group for primary amino group or secondary amino group in Y<sup>1</sup> has been removed is produced in some cases. The primary amino group or secondary amino group in Y may be protected again with a protective group (e.g. Boc or Cbz) by the same method as in the production process described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)).

4) Step 4

The compound (26-7) may be produced from the compound (26-6) by the same production process as described in the step 6 in the production process 1.

Production Process 27

A compound of the formula (27-4) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:



wherein  $R^6$  and  $Y$  are as defined in the item [1];  $Y^1$  is as defined in the production process 1;  $M^2$  is as defined in the production process 10;  $R^{88}$  is an alkyl group; and  $R^{89}$  is "an optionally substituted alkoxy group", "an optionally substituted amino group", "an optionally substituted aryloxy group", "an optionally substituted alkylthio group" or "an optionally substituted arylthio group".

1) Step 1

10 A compound (27-2) may be produced from a compound (26-4) by the same production process as described in literature (for example, Synlett 11, 1670 (2000), Tetrahedron Lett. 34, 6127 (1998) and J. Org. Chem. 58, 3387 (1993)).

15 2) Step 2

A compound (27-3) may be produced from the compound (27-2) by the same production process as described in literature (for example, J. Heterocycl.

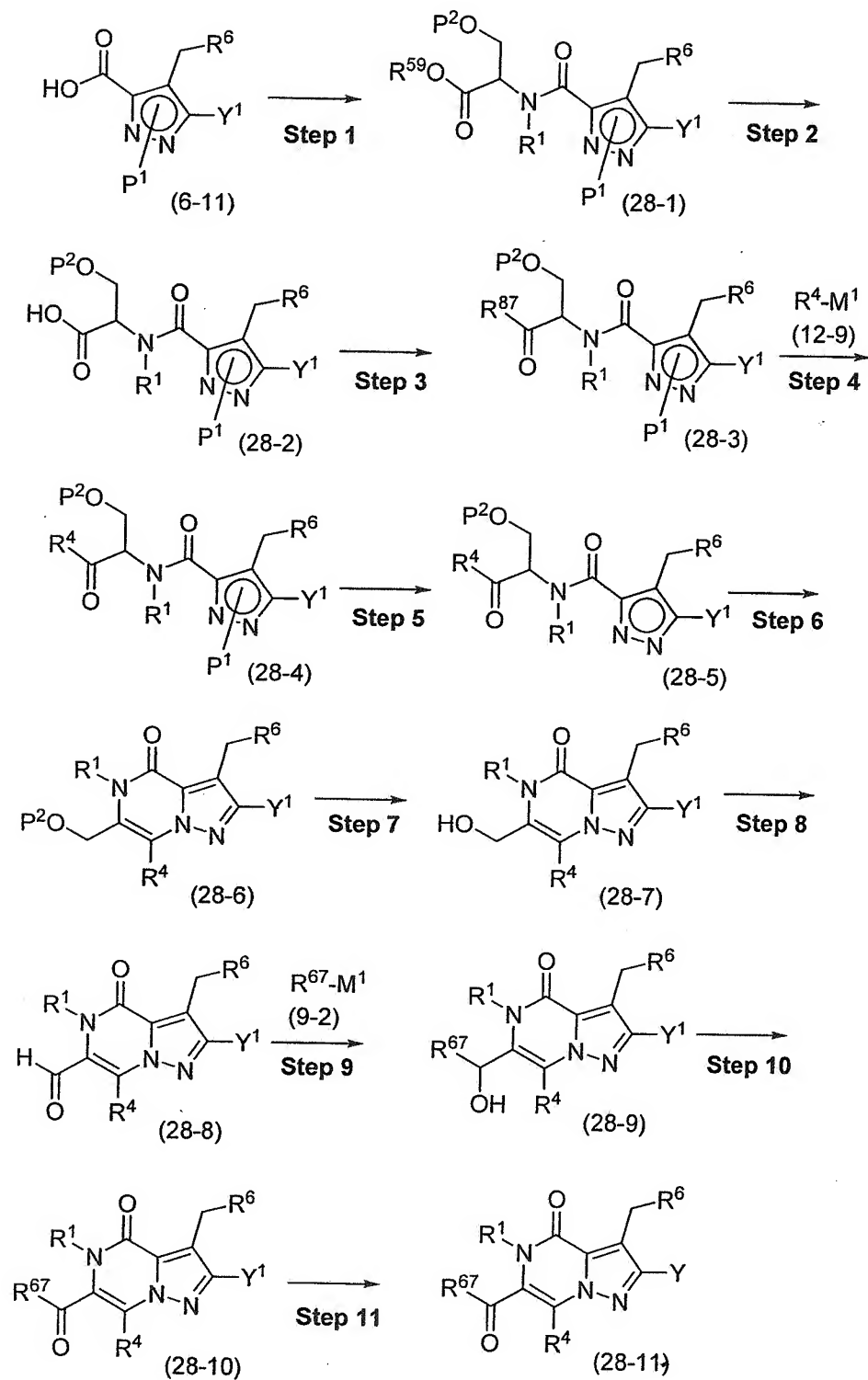
Chem. 39, 97 (2002), Eur. J. Med. Chem. 27, 251 (1992)  
and J. Med. Chem. 38, 3558 (1995)).

3) Step 3

The compound (27-4) may be produced from the  
5 compound (27-3) by the same production process as  
described in the step 6 in the production process 1.

Production Process 28

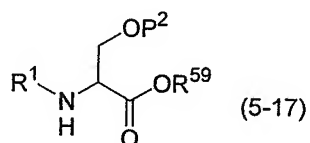
A compound of the formula (28-11) as the  
compound of the formula (I), or a salt thereof is  
10 produced, for example, by the following process:



wherein  $R^1$ ,  $R^4$ ,  $R^6$  and  $Y$  are as defined in the item [1];  
 $Y^1$  is as defined in the production process 1;  $R^{67}$ ,  $R^{87}$   
 and  $M^1$  are as defined in the production process 9;  $R^{59}$   
 and  $P^2$  are as defined in the production process 5; and  
 5  $P^1$  is as defined in the production process 6.

1) Step 1

A compound (28-1) may be produced from a  
 compound (6-11) and a compound (5-17) represented by  
 the formula:



10 wherein  $R^1$ ,  $R^{59}$  and  $P^2$  are as defined above, by the same  
 production process as described in the step 3, (3) in  
 the production process 1.

2) Step 2

A compound (28-2) may be produced from the  
 15 compound (28-1) by the same production process as  
 described in the step 3, (2) in the production process  
 1.

3) Step 3 to Step 4

A compound (28-4) may be produced from the  
 20 compound (28-2) by the same production process as  
 described in the step 1 to step 2 in the production  
 process 9.

4) Step 5

A compound (28-5) may be produced from the

compound (28-4) by the same process as that described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)) or the like.

5 5) Step 6

A compound (28-6) may be produced from the compound (28-5) by the same production process as described in the step 3, (4) in the production process 1.

10 In the reaction, a compound in which the protective group for primary amino group or secondary amino group in Y<sup>1</sup> has been removed is produced in some cases. The primary amino group or secondary amino group in Y may be protected again with a protective  
15 group (e.g. Boc or Cbz) by the same method as in the production process described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)).

6) Step 7

20 A compound (28-7) may be produced from the compound (28-6) by the same process as that described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)) or the like.

25 7) Step 8

A compound (28-8) may be produced from the compound (28-7) by the same production process as described in the step 11 in the production process 5.

## 8) Step 9 to Step 10

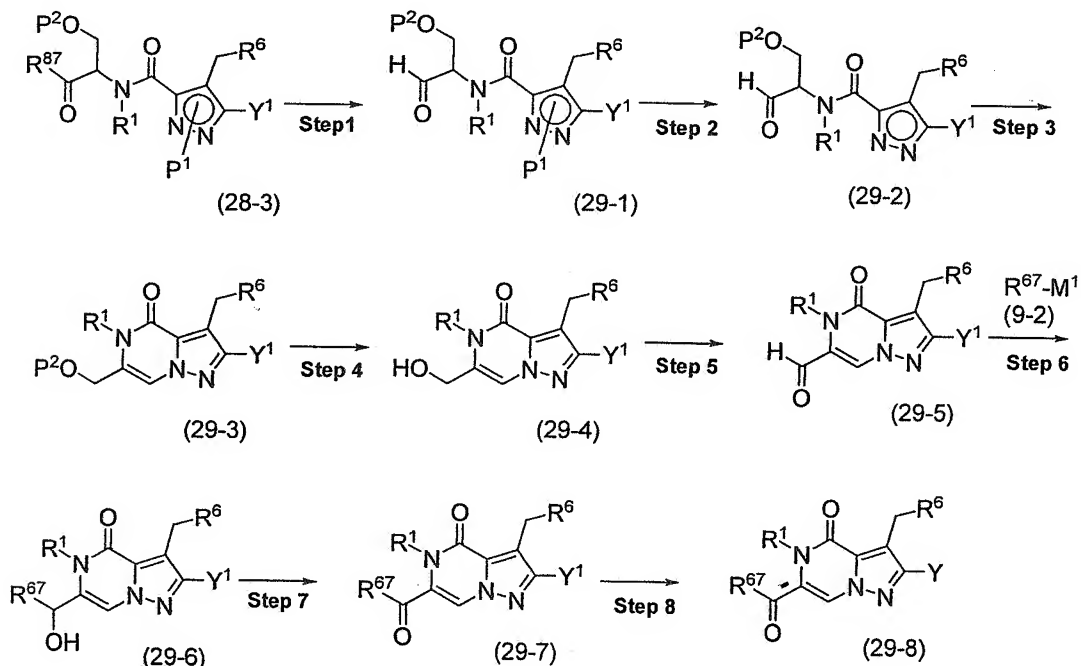
A compound (28-10) may be produced from the compound (28-8) by the same process as that described in literature (for example, R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., (1989)) or the like.

## 9) Step 11

The compound (28-11) may be produced from the compound (28-10) by the same production process as described in the step 6 in the production process 1.

## Production Process 29

A compound of the formula (29-8) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:



wherein  $R^1$ ,  $R^6$  and  $Y$  are as defined in the item [1];  $Y^1$  is as defined in the production process 1;  $R^{67}$ ,  $R^{87}$  and  $M^1$  are as defined in the production process 9;  $R^{59}$  and  $P^2$  are as defined in the production process 5; and  $P^1$  is as  
5 defined in the production process 6.

1) Step 1

A compound (29-1) may be produced from a compound (28-3) by the same production process as described in the step 6 in the production process 5.

10 2) Step 2

A compound (29-2) may be produced from the compound (29-1) by the same process as that described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons,  
15 Inc.)) or the like.

3) Step 3

A compound (29-3) may be produced from the compound (29-2) by the same production process as described in the step 3, (4) in the production process  
20 1.

In the reaction, a compound in which the protective group for primary amino group or secondary amino group in  $Y^1$  has been removed is produced in some cases. The primary amino group or secondary amino  
25 group in  $Y$  may be protected again with a protective group (e.g. Boc or Cbz) by the same method as in the production process described in literature (for example, Protective Groups in Organic Synthesis 2nd

Edition (John Wiley & Sons, Inc.)).

4) Step 4

A compound (29-4) may be produced from the compound (29-3) by the same process as that described in literature (for example, Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.)) or the like.

5) Step 5

A compound (29-5) may be produced from the compound (29-4) by the same production process as described in the step 11 in the production process 5.

6) Step 6 to Step 7

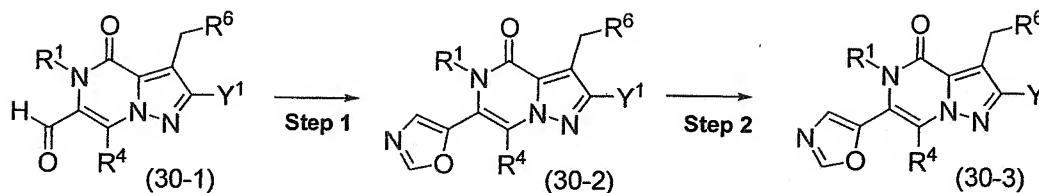
A compound (29-7) may be produced from the compound (29-5) by the same process as that described in literature (for example, R.C. Ralock, "Comprehensive Organic transformation", VCH publisher Inc., (1989)) or the like.

7) Step 8

The compound (29-8) may be produced from the compound (29-7) by the same production process as described in the step 6 in the production process 1.

Production Process 30

A compound of the formula (30-3) as the compound of the formula (I), or a salt thereof is produced, for example, by the following process:



wherein  $R^1$ ,  $R^4$ ,  $R^6$  and  $Y$  are as defined in the item [1];  
 $Y^1$  is as defined in the production process 1; and the  
 compound of the formula (30-1) corresponds to the  
 compound (28-8) described in the production process 28

5 or the compound (29-5) described in the production  
 process 29.

#### 1) Step 1

A compound (30-2) may be produced from a  
 compound (30-1) by the same production process as  
 10 described in literature (for example, Bioorg. Med.  
 Chem. Lett. 12, 2879 (2002)).

#### 2) Step 2

The compound (30-3) may be produced from the  
 compound (30-2) by the same production process as  
 15 described in the step 6 in the production process 1.

Unless otherwise specified, the starting  
 materials, reagents and the like used above may be  
 commercial compounds or may be produced from well-known  
 compounds by well-known processes.

20 In each of the production processes described  
 above, when the starting compound in each reaction has  
 a reactive group such as hydroxyl group, amino group or  
 carboxyl group, the reactive group in a site other than

a site where the reaction is desired is previously protected with a suitable protective group if necessary, and the protective group is removed after carrying out each reaction or after carrying out several reactions, whereby a desired compound may be obtained. As the protective group for protecting hydroxyl group, amino group, carboxyl group or the like, conventional protective groups used in the field of organic synthetic chemistry may be used. The introduction and removal of such a protective group may be carried out according to a conventional method (for example, the method described in T.W. Greene, P.G.M. Wuts, "Protective Groups in Organic Synthesis" 2nd Edition, John Wiley & Sons, Inc. (1991)).

For example, the protective group for the hydroxyl group includes tert-butyldimethylsilyl group, methoxymethyl group, tetrahydropyranyl group and the like. The protective group for the amino group includes tert-butoxycarbonyl group, benzyloxycarbonyl group and the like. The protective group for the hydroxyl group may be removed by reaction in a solvent such as aqueous methanol, aqueous ethanol or aqueous tetrahydrofuran in the presence of an acid such as hydrochloric acid, sulfuric acid or acetic acid. In the case of tert-butyldimethylsilyl group, it is also possible to carry out the removal in a solvent such as tetrahydrofuran in the presence of, for example, tetrabutylammonium fluoride. In the case of tert-

butoxycarbonyl group, the protective group for the amino group may be removed, for example, by reaction in a solvent such as aqueous tetrahydrofuran, methylene chloride, chloroform or aqueous methanol in the presence of an acid such as hydrochloric acid or trifluoroacetic acid. In the case of benzyloxycarbonyl group, the removal may be carried out, for example, by reaction in a solvent such as acetic acid in the presence of an acid such as hydrobromic acid.

As a form in which the carboxyl group is protected, tert-butyl esters, orthoesters and acid amides are exemplified. Such a protective group is removed as follows. In the case of the tert-butyl ester, the removal is carried out, for example, by reaction in an aqueous solvent in the presence of hydrochloric acid. In the case of the orthoester, the removal is carried out, for example, by treatment with an acid and then an alkali such as sodium hydroxide in a solvent such as aqueous methanol, aqueous tetrahydrofuran or aqueous 1,2-dimethoxyethane. In the case of the acid amide, the removal is carried out by reaction in a solvent such as water, aqueous methanol or aqueous tetrahydrofuran in the presence of an acid such as hydrochloric acid or sulfuric acid.

The bicyclic pyrazole derivative of the formula (I) includes those having a center of optical activity. The compound having a center of optical activity may be obtained as a racemic modification, or

it may be obtained as an optically active substance when an optically active starting material is used. If necessary, the racemic modification obtained may be physically or chemically resolved into optical

5 antipodes by a well-known method. Preferably, diastereomers are formed from the racemic modification by a reaction using a reagent for optical resolution. The diastereomers different in form may be resolved by a well-known method such as fractional crystallization.

10           The bicyclic pyrazole derivative or prodrug thereof of the present invention may be converted to a salt, for example, by mixing with a pharmaceutically acceptable acid in a solvent such as water, methanol, ethanol or acetone. The pharmaceutically acceptable  
15 acid includes, for example, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, etc.; and organic acids such as acetic acid, propionic acid, oxalic acid, succinic acid, lactic acid, malic acid, tartaric acid,  
20 citric acid, maleic acid, fumaric acid, methanesulfonic acid, p-toluenesulfonic acid, ascorbic acid, etc.

The agents of the present invention are expected to be usable for the treatment of various diseases because of their inhibitory effect on DPP-IV.

25 The compounds described in the present specification are useful for the suppression of postprandial hyperglycemia in a prediabetic, the treatment of non-insulin-dependent diabetes mellitus, the treatment of

autoimmune diseases such as arthritis and articular rheumatism, the treatment of intestinal mucosa diseases, growth acceleration, the inhibition of rejection of a transplantate, the treatment of

5 corpulence, the treatment of eating disorder, the treatment of HIV infection, the suppression of cancer metastasis, the treatment of prostatomegaly, the treatment of periodontitis, and the treatment of osteoporosis.

10               When used for the treatment, the bicyclic pyrazole derivative of the present invention, the prodrug thereof or the pharmaceutically acceptable salt of the derivative or prodrug may be administered as a pharmaceutical composition orally or parenterally (for

15 example, by intravenous, subcutaneous or intramuscular injection, locally, intrarectally, percutaneously, or through nose). Compositions for the oral administration include, for example, tablets, capsules, pills, granules, powders, solutions and suspensions.

20 Compositions for the parenteral administration include, for example, aqueous or oily preparations for injection, ointments, creams, lotions, aerosols, suppositories and patches. These pharmaceutical compositions are prepared by conventional techniques

25 and may contain non-toxic and inactive carriers or excipients conventionally used in the field of formulation.

Although the dose is varied depending on the

individual compounds, the disease, age, body weight and sex of a patient, symptom, administration route and the like, the bicyclic pyrazole derivative of the present invention, the prodrug thereof or the pharmaceutically acceptable salt of the derivative or prodrug is administered in a dose of 0.1 to 1000 mg/day, preferably 1 to 300 mg/day in one portion or two or three portions a day. It is also possible to administer the derivative, prodrug or salt at intervals of several days to several weeks.

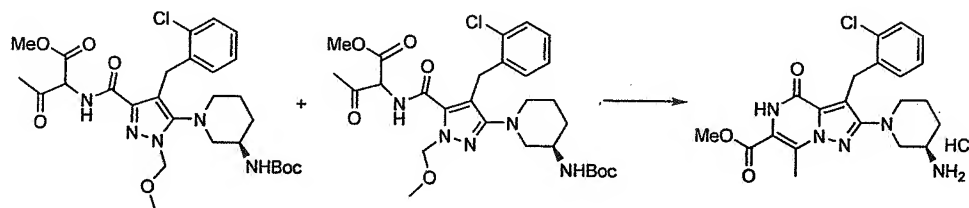
The bicyclic pyrazole derivative of the present invention, the prodrug thereof or the pharmaceutically acceptable salt of the derivative or prodrug may be used in combination with other remedies for diabetes.

#### EXAMPLES

The present invention is more concretely illustrated below with reference examples, working examples and test examples, which should not be construed as limiting the scope of the invention. The nomenclature of compounds shown in the reference examples and working examples mentioned below is not always based on IUPAC. Abbreviations are used in these examples for the simplification of description in some cases and they have the same meanings as defined above.

#### Example 1

Methyl 2-[(3R)-3-aminopiperidin-1-yl]-3-(2-chlorobenzyl)-7-methyl-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazine-6-carboxylate hydrochloride



A methyl 2-([5-{(3R)-3-[(tert-butoxy-  
5 carbonyl)amino]piperidin-1-yl}-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazol-3-yl]carbonyl)amino)-3-oxobutanate mixture (55.0 mg) was dissolved in a 4N hydrochloric acid/1,4-dioxane solution (1.5 ml), followed by adding thereto water (0.5 ml), and the  
10 resulting mixture was stirred at 50°C for 2 hours. The reaction solution was concentrated under reduced pressure and the water remaining in the resulting residue was distilled off as an azeotrope with methanol to obtain the title compound (42.0 mg).

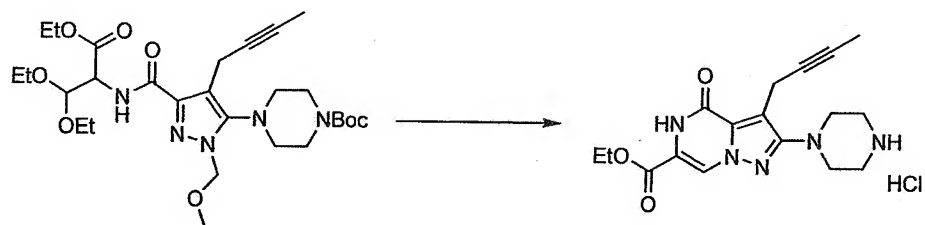
15 <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 10.74 (s, 1H), 8.23 (bs, 3H), 7.50-7.35 (m, 1H), 7.30-7.05 (m, 2H), 7.05-6.80 (m, 1H), 4.35 (s, 2H), 3.83 (s, 3H), 3.80-3.60 (m, 1H), 3.20-2.90 (m, 2H), 2.75 (s, 3H), 2.65-2.40 (m, 2H), 2.00-1.80 (m, 1H), 1.70-1.20 (m, 3H).

20 MS (ESI+) 430 (M<sup>+</sup>+1, 100%).

#### Example 2

Ethyl 3-but-2-yn-1-yl-4-oxo-2-piperazin-1-yl-

4,5-dihydropyrazolo[1,5-a]pyrazine-6-carboxylate  
hydrochloride



To a solution of tert-butyl 4-[4-but-2-yn-1-yl-3-({[1-diethoxymethyl]-2-ethoxy-2-oxoethyl}amino)carbonyl]-1-(methoxymethyl)-1H-pyrazol-5-yl]pyrazol-5-yl]piperazin-1-carboxylate (136 mg) in 1,4-dioxane (1 ml) were added 4N hydrochloric acid (2 ml) and water (1 ml), and the resulting mixture was stirred with heating at 50°C for two and a half hours.

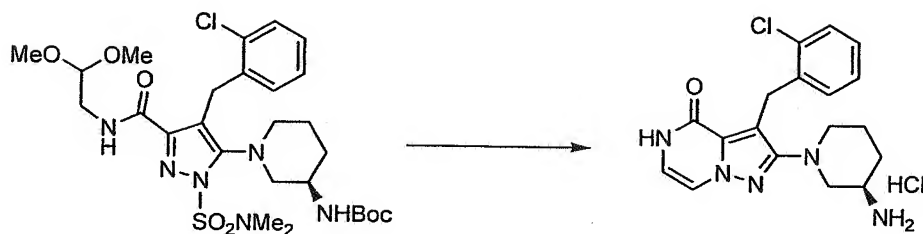
The reaction mixture was concentrated under reduced pressure to obtain the title compound (77 mg).

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 9.16 (bs, 2H), 8.11 (s, 1H), 4.29 (q, J = 7.2 Hz, 2H), 3.88-3.87 (bs, 2H), 3.57-3.50 (m, 4H), 3.28-3.24 (m, 4H), 1.76 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H).

MS (ESI+) 344 (M<sup>+</sup>+1, 100%).

Example 3

2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)pyrazolo[1,5-a]pyrazin-4(5H)-one  
hydrochloride



Water (20 ml) and a 4N hydrochloric acid/1,4-dioxane solution (40 ml) were added to a solution of tert-butyl ((3R)-1-{4-(2-chlorobenzyl)-3-[(2,2-dimethoxyethyl)amino]carbonyl}-1-[(dimethylamino)sulfonyl]-1H-pyrazol-5-yl)piperidin-3-yl)carbamate (2.97 g) in 1,4-dioxane (20 ml), and the resulting mixture was stirred at 50°C for 2 hours. After cooling to 0°C, dioxane (30 ml), water (20 ml) and sodium hydrogencarbonate (30 mg) were added thereto. The resulting mixture was warmed to room temperature and di-tert-butyl dicarbonate (2.06 g) was added thereto and stirred overnight. The 1,4-dioxane was distilled off under reduced pressure and water (100 ml) was added to the residue, followed by two runs of extraction with ethyl acetate (100 ml). The combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (chloroform/ethyl acetate = 1/1) to obtain a purified substance (1.30 g). MS (ESI+) 458 ( $M^+ + 1$ , 36%).

Then, a 4N hydrochloric acid/1,4-dioxane solution (1.0 ml) was added to a suspension (0.1 ml) of

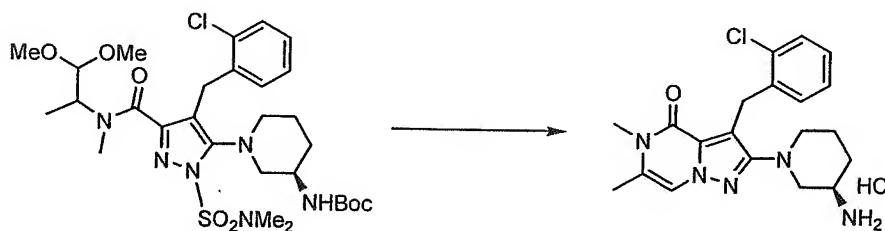
the purified substance (53.0 mg) in 1,4-dioxane, and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to obtain the title compound as a crude product (47.8 mg).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 11.08 (d,  $J = 5.2\text{Hz}$ , 1H), 8.00–7.98 (m, 3H), 7.50–7.43 (m, 2H), 7.22–7.19 (m, 2H), 6.99–6.96 (m, 1H), 6.73–6.70 (m, 1H), 4.28 (s, 2H), 3.25–3.22 (m, 1H), 2.94–2.91 (m, 2H), 2.55–2.53 (m, 2H), 2.33–2.31 (m, 1H), 1.91–1.90 (m, 1H), 1.41–1.39 (m, 2H).

MS (ESI+) 358 ( $\text{M}^+ + 1$ , 28%).

#### Example 4

2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5,6-dimethylpyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride



Water (1.0 ml) and a 4N hydrochloric acid/1,4-dioxane solution (2.0 ml) were added to a solution of tert-butyl ((3R)-1-{4-(2-chlorobenzyl)-3-[[2,2-dimethoxy-1-methylethyl] (methyl)amino]carbonyl}-1-[(dimethylamino)sulfonyl]-1H-pyrazol-5-yl}piperidin-3-yl)carbamate (126 mg) in 1,4-dioxane (1.0 ml), and

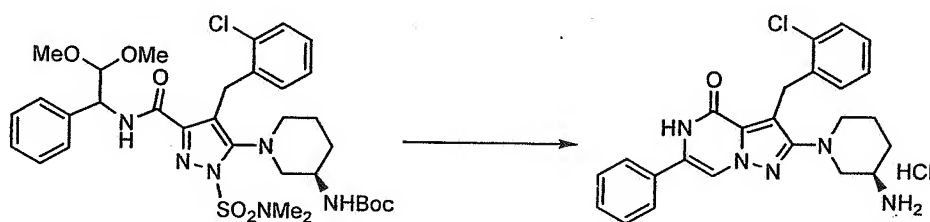
the resulting mixture was stirred at 50°C for 2 hours. After cooling to 0°C, 1,4-dioxane (1.0 ml), water (1.0 ml) and sodium hydrogencarbonate (1.5 g) were added thereto. The resulting mixture was warmed to room temperature and di-tert-butyl dicarbonate (83.8 mg) was added thereto and stirred overnight. The 1,4-dioxane was distilled off under reduced pressure and water (10 ml) was added to the residue, followed by two runs of extraction with ethyl acetate (10 ml). The combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 1/1) to obtain a purified substance (56.7 mg). A 4N hydrochloric acid/1,4-dioxane solution (1.0 ml) was added to a suspension (0.1 ml) of the purified substance (53.0 mg) in 1,4-dioxane, and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to obtain the title compound as a crude product (51.9 mg).

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 8.09-8.06 (m, 3H), 7.52 (s, 1H), 7.45-7.42 (m, 1H), 7.23-7.15 (m, 2H), 6.92-6.89 (m, 1H), 4.26 (s, 2H), 3.55-3.51 (m, 1H), 3.34 (s, 3H), 3.28-3.25 (m, 1H), 2.99-2.90 (m, 2H), 2.67-2.63 (m, 1H), 2.26 (s, 3H), 1.98-1.95 (m, 1H), 1.75-1.70 (m, 1H), 1.46-1.41 (m, 2H).

MS (ESI+) 386 ( $M^+ + 1$ , 35%).

## Example 5

2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-6-phenylpyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride



5 Water (2.0 ml) and a 4N hydrochloric acid/1,4-dioxane solution (4.0 ml) were added to a solution of tert-butyl ((3R)-1-{4-(2-chlorobenzyl)-3-  
 10 {[(2,2-dimethoxy-1-phenylethyl)amino]carbonyl}-1-  
 [(dimethylamino)sulfonyl]-1H-pyrazol-5-yl}piperidin-3-  
 15 yl)carbamate (270 mg) in 1,4-dioxane (2.0 ml), and the resulting mixture was stirred at 50°C for 2 hours. After cooling to 0°C, dioxane (3.0 ml), water (1.0 ml) and sodium hydrogencarbonate (3.0 g) were added thereto. The resulting mixture was warmed to room  
 20 temperature and di-tert-butyl dicarbonate (167 mg) was added thereto and stirred overnight. The 1,4-dioxane was distilled off under reduced pressure and water (10 ml) was added to the residue, followed by two runs of extraction with ethyl acetate (10 ml). The combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 2/1) to obtain a purified substance (94.3 mg). A 4N

hydrochloric acid/1,4-dioxane solution (1.0 ml) was added to a suspension (0.1 ml) of the purified substance (92.0 mg) in 1,4-dioxane, and the resulting mixture was stirred at room temperature for 1 hour.

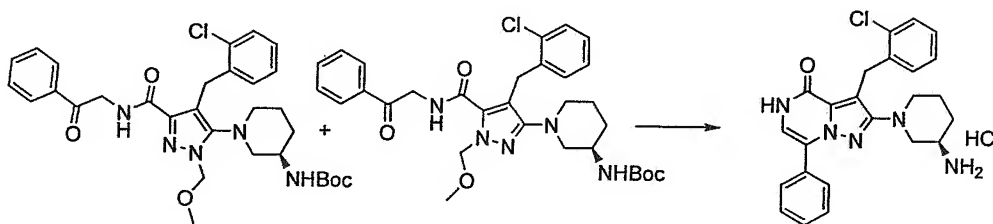
- 5 The reaction mixture was concentrated under reduced pressure to obtain the title compound as a crude product (72.8 mg).

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 11.4 (s, 1H), 8.15-8.12 (m, 3H), 7.93 (s, 1H), 7.74-7.71 (m, 2H), 7.49-7.42 (m, 4H), 7.25-7.21 (m, 2H), 7.09-7.03 (m, 1H), 4.33 (s, 2H), 3.25-3.21 (m, 1H), 2.96-2.93 (m, 2H), 2.53-2.48 (m, 2H), 1.69-1.65 (m, 1H), 1.66-1.47 (m, 1H), 1.45-1.23 (m, 2H).

MS (ESI+) 434 (M<sup>+</sup>+1, 35%).

# 15 Example 6

2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-7-phenylpyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride



- Water (2.0 ml) and a 4N hydrochloric acid/1,4-dioxane solution (4.0 ml) were added to a solution of a tert-butyl [(3R)-1-(4-(2-chlorobenzyl)-1-(methoxymethyl)-3-[(2-oxo-2-phenylethyl)amino]-

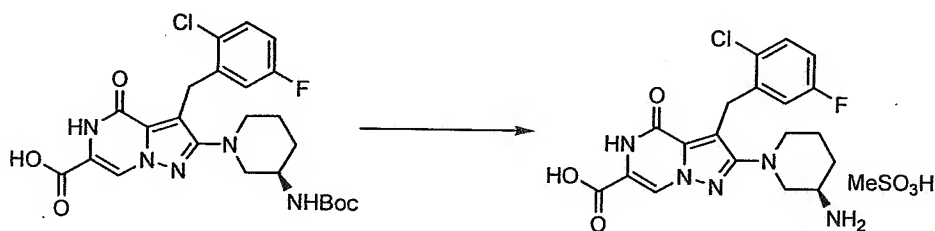
carbonyl}-1H-pyrazol-5-yl)piperidin-3-yl]carbamate mixture (150 mg) in 1,4-dioxane (2.0 ml), and the resulting mixture was stirred at 50°C for 2 hours. After cooling to 0°C, 1,4-dioxane (3.0 ml), water (1.0 ml) and sodium hydrogencarbonate (3.0 g) were added thereto. The resulting mixture was warmed to room temperature and di-tert-butyl dicarbonate (65.8 mg) was added thereto and stirred overnight. The 1,4-dioxane was distilled off under reduced pressure and water (20 ml) was added to the residue, followed by two runs of extraction with ethyl acetate (20 ml). The combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 2/1) to obtain a purified substance (54.8 mg). A 4N hydrochloric acid/1,4-dioxane solution (1.0 ml) was added to a suspension (0.1 ml) of the purified substance (54.8 mg) in 1,4-dioxane, and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to obtain the title compound as a crude product (47.9 mg).

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 11.40-11.38 (d, J = 5.9Hz, 1H), 8.06-8.04 (m, 3H), 7.81-7.79 (m, 2H), 7.48-7.44 (m, 4H), 7.24-7.21 (m, 2H), 7.06-7.04 (m, 1H), 6.85-6.84 (m, 1H), 4.35 (s, 2H), 3.52-3.51 (m, 1H), 3.05-2.90 (m, 2H), 2.75-2.71 (m, 2H), 1.89-1.86 (m, 1H), 1.65-1.64 (m, 1H), 1.44-1.40 (m, 2H).

MS (ESI+) 434 ( $M^+ + 1$ , 31%).

### Example 7

2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chloro-5-fluorobenzyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazine-6-carboxylic acid methanesulfonate



Methanesulfonic acid (214 mg) was added to a solution of 2-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-3-(2-chloro-5-fluorobenzyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazine-6-carboxylic acid (580 mg) in chloroform (10 ml), and the resulting mixture was stirred at 50°C for 2 hours. After the mixture was allowed to cool, the chloroform was distilled off under reduced pressure and the resulting solid was recrystallized from 2-propanol. The solid thus obtained was collected by filtration and washed with 2-propanol to obtain the title compound (380 mg) as a white solid.

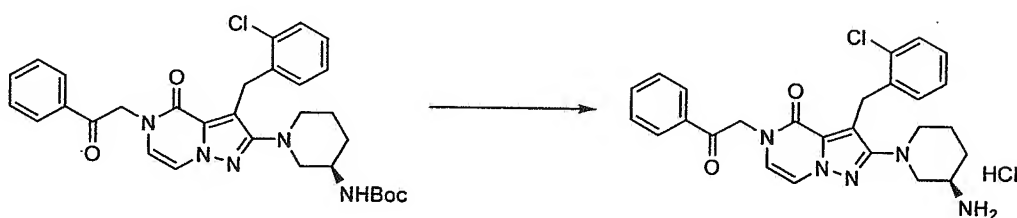
$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 8.13 (s, 1H), 7.45–7.39 (m, 1H), 6.99–6.93 (m, 1H), 6.77–6.71 (m, 1H), 4.44 (d,  $J = 17\text{Hz}$ , 1H), 4.36 (d,  $J = 17\text{ Hz}$ , 1H), 3.72–3.62 (m, 1H), 3.39–3.30 (m, 1H), 3.14–3.02 (m, 2H), 3.86–3.73 (m, 1H), 2.68 (s, 3H), 2.07–1.95 (m, 1H), 1.78–1.67 (m,

1H), 1.62-1.47 (m, 2H).

MS (ESI+) 420 ( $M^+ + 1$ , 33%).

# Example 8

2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-(2-oxo-2-phenylethyl)pyrazolo[1,5-a]pyrazin-4(5H)-one hydrochloride

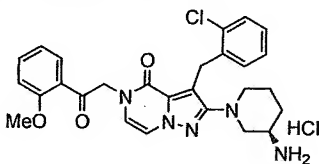
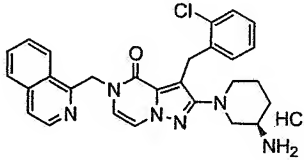
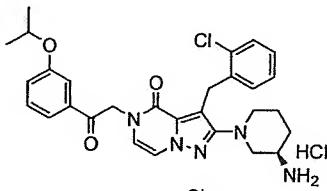
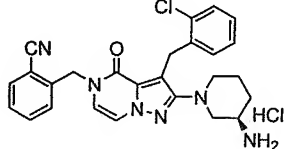
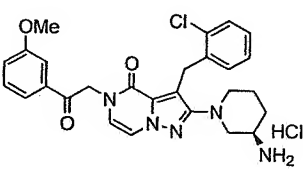
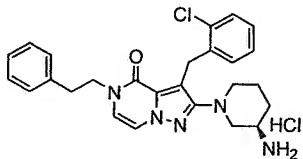
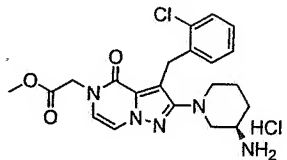
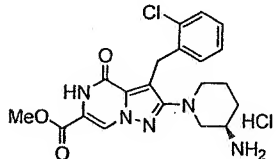


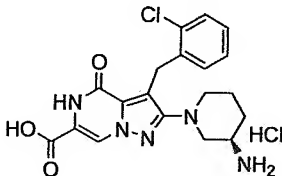
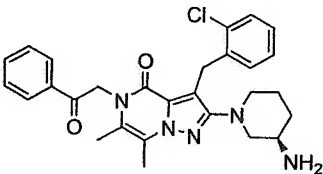
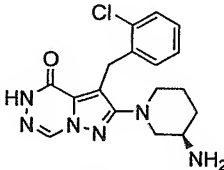
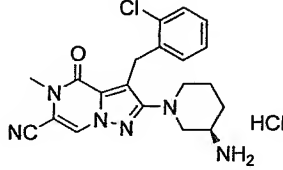
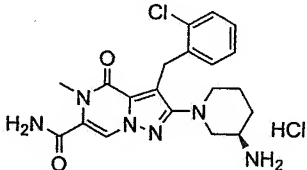
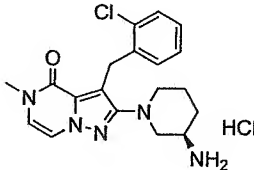
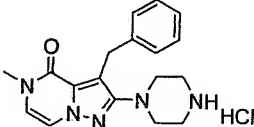
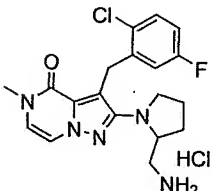
A 4N hydrochloric acid/1,4-dioxane solution (1.0 ml) was added to a suspension (0.1 ml) of tert-butyl {(3R)-1-[3-(2-chlorobenzyl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydropyrazolo[1,5-a]pyrazin-2-yl]piperidin-3-yl}carbamate (38.8 mg) in 1,4-dioxane, and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to obtain the title compound as a crude product (38.9 mg).

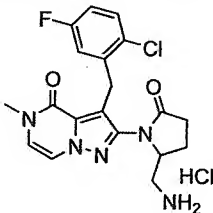
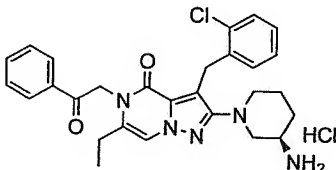
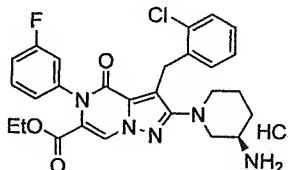
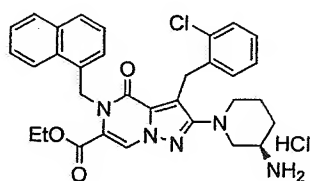
$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 8.06-8.04 (m, 5H), 7.73-7.69 (m, 2H), 7.62-7.58 (m, 2H), 7.45-7.42 (m, 1H), 7.22-7.20 (m, 2H), 7.00 (d,  $J = 6.0\text{Hz}$ , 1H), 6.95-6.93 (m, 1H), 5.47 (s, 2H), 4.28 (s, 2H), 3.55-3.51 (m, 1H), 3.25-3.20 (m, 1H), 3.10-2.91 (m, 2H), 2.85-2.75 (m, 1H), 2.01-1.95 (m, 1H), 1.75-1.69 (m, 1H), 1.51-1.45 (m, 2H).

MS (ESI+) 476 ( $M^+1$ , 46%).

The following compounds of Example 9 to Example 28 were synthesized by the same process as in Example 8.

Example number		Reference example number for starting material
Example 9		Reference Example 12-1
Example 10		Reference Example 12-3
Example 11		Reference Example 12-2
Example 12		Reference Example 12-4
Example 13		Reference Example 12-5
Example 14		Reference Example 12-6
Example 15		Reference Example 12-7
Example 16		Reference Example 10

Example number		Reference example number for starting material
Example 17		Reference Example 11
Example 18		Reference Example 25
Example 19		Reference Example 29
Example 20		Reference Example 15
Example 21		Reference Example 16
Example 22		Reference Example 13
Example 23		Reference Example 19
Example 24		Reference Example 36

Example number		Reference example number for starting material
Example 25		Reference Example 37
Example 26		Reference Example 33
Example 27		Reference Example 9
Example 28		Reference Example 91

## Example 9

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 8.31-8.21 (m, 3H), 7.77-7.75 (m, 1H), 7.67-7.65 (m, 2H), 7.44-7.42 (m, 1H), 7.28-7.19 (m, 3H), 7.11-7.09 (m, 1H), 7.03-7.01 (m, 1H), 7.00-6.94 (m, 1H), 5.24 (s, 2H), 4.28 (s, 2H), 3.97 (s, 3H), 3.72-3.68 (m, 1H), 3.20-3.11 (m, 1H), 3.05-2.95 (m, 2H), 2.70-2.68 (m, 1H), 1.95-1.85 (m, 1H), 1.71-1.65 (m, 1H), 1.55-1.35 (m, 2H).  
MS (ESI+) 506 ( $M^+ + 1$ , 73%).

## 10 Example 10

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 8.44 (d,  $J = 8.4\text{Hz}$ , 1H), 8.40 (d,  $J = 5.9\text{Hz}$ , 1H), 8.21-8.11 (m, 4H), 7.96-7.94 (m, 2H), 7.84-7.80 (m, 1H), 7.71 (d,  $J = 5.9\text{Hz}$ , 1H), 7.43-7.41 (m, 1H), 7.21-7.18 (m, 2H), 7.13 (d,  $J = 5.9\text{Hz}$ , 1H), 7.02-6.99 (m, 1H), 5.84 (s, 2H), 4.22 (s, 2H), 3.19-3.16 (m, 1H), 3.02-2.91 (m, 2H), 2.61-2.53 (m, 2H), 1.92-1.91 (m, 1H), 1.68-1.65 (m, 1H), 1.46-1.40 (m, 2H).  
MS (ESI+) 499 ( $M^+ + 1$ , 100%).

## 20 Example 11

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 8.06-8.03 (m, 3H), 7.67 (d,  $J = 5.9\text{Hz}$ , 1H), 7.59 (d,  $J = 8.0\text{Hz}$ , 1H), 7.50-7.42 (m, 3H), 7.28-7.27 (m, 1H), 7.22-7.19 (m, 2H), 6.98 (d,  $J = 5.9\text{Hz}$ , 1H), 6.96-6.92 (m, 1H), 5.44 (s, 2H), 4.75-4.69 (m, 1H), 4.27 (s, 2H), 3.30-3.28 (m, 1H), 3.15-3.11 (m, 1H), 3.05-2.98 (m, 1H), 2.52-2.45 (m, 2H),

2.10-2.07 (m, 1H), 1.91-1.90 (m, 1H), 1.67-1.42 (m, 2H), 1.28 (d,  $J = 6.0\text{Hz}$ , 6H).

MS (ESI+) 534 ( $M^+ + 1$ , 80%).

#### Example 12

5  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 8.13-8.10 (m, 3H), 7.88 (d,  $J = 7.7\text{Hz}$ , 1H), 7.72 (d,  $J = 6.0\text{Hz}$ , 1H), 7.69-7.65 (m, 1H), 7.52-7.48 (m, 1H), 7.43 (d,  $J = 7.7\text{Hz}$ , 1H), 7.26-7.17 (m, 3H), 7.10 (d,  $J = 6.0\text{Hz}$ , 1H), 7.00-6.97 (m, 1H), 5.25 (s, 2H), 4.27 (s, 2H), 3.19-3.16 (m, 1H), 10 3.01-2.88 (m, 2H), 2.60-2.51 (m, 2H), 1.93-1.90 (m, 1H), 1.67-1.60 (m, 1H), 1.47-1.41 (m, 2H).

MS (ESI+) 473 ( $M^+ + 1$ , 66%).

#### Example 13

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 8.15-8.11 (m, 3H), 7.68 (d,  $J = 5.9\text{Hz}$ , 1H), 7.65-7.63 (m, 1H), 7.53-7.48 (m, 15 2H), 7.44-7.41 (m, 1H), 7.32-7.29 (m, 1H), 7.21-7.18 (m, 2H), 7.00 (d,  $J = 5.9\text{Hz}$ , 1H), 6.95-6.93 (m, 1H), 5.45 (s, 2H), 4.27 (s, 2H), 3.83 (s, 3H), 3.61-3.57 (m, 1H), 3.25-3.20 (m, 1H), 3.04-2.91 (m, 2H), 2.66-2.63 20 (m, 1H), 1.92-1.88 (m, 1H), 1.68-1.65 (m, 1H), 1.48-1.40 (m, 2H).

MS (ESI+) 506 ( $M^+ + 1$ , 89%).

#### Example 14

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 8.09-8.03 (m, 3H), 7.57 (d,  $J = 5.9\text{Hz}$ , 1H), 7.45 (dd,  $J = 1.9\text{Hz}$ , 7.7Hz, 1H), 25

7.30-7.20 (m, 7H), 6.94 (d,  $J = 5.9\text{Hz}$ , 1H), 6.89 (dd,  $J = 1.6\text{Hz}$ , 7.1Hz, 1H), 4.29 (s, 2H), 4.04 (t,  $J = 6.8\text{Hz}$ , 2H), 3.55-3.50 (m, 1H), 3.20-3.14 (m, 1H), 2.95-2.89 (m, 4H), 2.57-2.55 (m, 1H), 1.91-1.89 (m, 1H), 1.66-1.64 (m, 1H), 1.45-1.41 (m, 2H).

MS (ESI+) 462 ( $M^+ + 1$ , 37%).

## Example 15

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 8.18-8.16 (m, 3H), 7.67 (d,  $J = 5.9\text{Hz}$ , 1H), 7.46-7.44 (m, 1H), 7.22-7.19 (m, 2H), 7.03-6.97 (m, 2H), 4.68 (s, 2H), 4.28 (s, 2H), 3.68 (s, 3H), 3.52-3.44 (m, 1H), 3.18-3.16 (m, 1H), 3.03-2.89 (m, 2H), 2.62-2.60 (m, 1H), 1.92-1.90 (m, 1H), 1.67-1.64 (m, 1H), 1.45-1.41 (m, 2H).

MS (ESI+) 430 ( $M^+ + 1$ , 44%).

## 15 Example 16

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 8.30 (bs, 1H), 8.19 (s, 1H), 7.46 (dd,  $J = 1.7\text{Hz}$ , 7.7Hz, 1H), 7.27-7.18 (m, 2H), 7.00 (dd,  $J = 1.7\text{Hz}$ , 7.3Hz, 1H), 4.39-4.29 (m, 2H), 3.84 (s, 3H), 3.62-3.60 (m, 1H), 3.39-3.29 (m, 3H), 3.17-3.15 (m, 1H), 3.06-3.03 (m, 1H), 2.96-2.91 (m, 1H), 2.61-2.52 (m, 1H), 1.91-1.88 (m, 1H), 1.66-1.62 (m, 1H), 1.47-1.37 (m, 2H).

MS (ESI+) 416 ( $M^+ + 1$ , 32%).

## Example 17

25  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 11.00 (s, 1H), 8.12-8.08

(m, 4H), 7.47-7.44 (m, 1H), 7.25-7.18 (m, 2H), 7.00-6.97 (m, 1H), 4.40-4.28 (m, 2H), 3.25-3.21 (m, 1H), 3.09-3.05 (m, 1H), 2.98-2.95 (m, 1H), 2.75-2.62 (m, 2H), 1.99-1.90 (m, 1H), 1.75-1.71 (m, 1H), 1.60-1.52 (m, 2H).

MS (ESI+) 402 ( $M^+ + 1$ , 35%).

#### Example 18

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 8.09-8.07 (m, 5H), 7.73-7.71 (m, 1H), 7.62-7.58 (m, 2H), 7.44-7.41 (m, 1H), 7.21-7.18 (m, 2H), 6.93-6.90 (m, 1H), 5.61 (s, 2H), 4.28 (s, 2H), 3.60-3.57 (m, 1H), 3.25-3.23 (m, 1H), 3.01-2.98 (m, 2H), 2.71-2.68 (m, 1H), 2.52 (s, 3H), 2.18 (s, 3H), 1.92-1.90 (m, 1H), 1.69-1.66 (m, 1H), 1.47-1.44 (m, 2H).

MS (ESI+) 504 ( $M^+ + 1$ , 86%).

#### Example 19

$^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 8.35 (s, 1H), 7.32-7.29 (m, 1H), 7.11-7.07 (m, 2H), 6.94-6.90 (m, 1H), 4.35 (d,  $J = 17.2\text{Hz}$ , 1H), 4.27 (d,  $J = 17.2\text{Hz}$ , 1H), 3.50-3.46 (m, 1H), 3.22-3.20 (m, 1H), 3.04-2.94 (m, 2H), 2.72-2.68 (m, 1H), 1.93-1.89 (m, 1H), 1.54-1.38 (m, 3H).

MS (ESI+) 359 ( $M^+ + 1$ , 36%).

#### Example 20

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 8.88 (s, 1H), 8.12 (bs, 3H), 7.47-7.45 (m, 1H), 7.25-7.17 (m, 2H), 6.97-6.95

(m, 1H), 4.33-4.32 (m, 2H), 3.65-3.62 (m, 1H), 3.43 (s, 3H), 3.15-3.14 (m, 1H), 3.07-3.04 (m, 1H), 2.96-2.91 (m, 1H), 2.63-2.61 (m, 1H), 1.92-1.88 (m, 1H), 1.64-1.63 (m, 1H), 1.47-1.33 (m, 2H).

5 MS (ESI+) 397 ( $M^+ + 1$ , 28%).

#### Example 21

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 8.20-8.17 (m, 4H), 7.89 (s, 1H), 7.80 (bs, 1H), 7.47-7.45 (m, 1H), 7.25-7.18 (m, 2H), 6.96-6.93 (m, 1H), 4.31 (s, 2H), 3.67-3.66 (m, 10 1H), 3.39 (s, 3H), 3.25-3.23 (m, 1H), 2.99-2.94 (m, 2H), 2.62-2.60 (m, 1H), 1.91-1.89 (m, 1H), 1.65-1.64 (m, 1H), 1.46-1.40 (m, 2H).

MS (ESI+) 415 ( $M^+ + 1$ , 35%).

#### Example 22

15  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 7.49 (d,  $J = 5.9\text{Hz}$ , 1H), 7.42-7.40 (m, 1H), 7.20-7.16 (m, 2H), 6.99 (d,  $J = 7.2\text{Hz}$ , 1H), 6.87 (d,  $J = 5.9\text{Hz}$ , 1H), 4.13 (s, 2H), 3.76-3.74 (m, 1H), 3.69-3.61 (m, 2H), 3.61-3.58 (m, 2H), 3.46 (s, 3H), 3.10-3.04 (m, 2H), 2.80-2.77 (m, 20 1H), 2.02-2.00 (m, 1H), 1.75-1.73 (m, 1H), 1.61-1.54 (m, 2H).

MS (ESI+) 372 ( $M^+ + 1$ , 38%).

#### Example 23

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 7.45 (d,  $J = 5.9\text{Hz}$ , 1H), 25 7.27-7.20 (m, 4H), 7.18-7.15 (m, 1H), 6.87 (d,  $J = 5.9$

Hz, 1H), 4.35 (s, 2H), 3.48 (s, 3H), 3.28 (t,  $J = 5.1$  Hz, 4H), 3.17 (t,  $J = 5.1$  Hz, 4H).

MS (ESI+) 324 ( $M^+ + 1$ , 100%).

#### Example 24

- 5  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 7.48 (d,  $J = 6.0$  Hz, 1H), 7.44-7.40 (m, 1H), 6.97-6.92 (m, 1H), 6.83 (d,  $J = 6.0$  Hz, 1H), 6.66-6.63 (m, 1H), 4.50 (s, 2H), 4.29-4.25 (m, 1H), 3.55-3.48 (m, 1H), 3.45 (s, 3H), 3.17-3.05 (m, 3H), 2.13-2.06 (m, 1H), 1.91-1.75 (m, 3H).
- 10 MS (ESI+) 390 ( $M^+ + 1$ , 100%).

#### Example 25

- $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 8.14 (br, 3H), 7.73 (d,  $J = 6.0$  Hz, 1H), 7.47-7.43 (m, 1H), 7.21 (d,  $J = 6.0$  Hz, 1H), 7.12-7.07 (m, 1H), 6.93-6.89 (m, 1H), 4.30 (d,  $J = 16.3$  Hz, 1H), 4.24 (d,  $J = 16.3$  Hz, 1H), 4.06-4.00 (m, 1H), 3.41 (s, 3H), 2.99-2.94 (m, 1H), 2.73-2.67 (m, 1H), 2.54-2.45 (m, 1H), 2.32-2.24 (m, 1H), 2.10-1.97 (m, 2H).
- 15 MS (ESI+) 404 ( $M^+ + 1$ , 100%).

#### 20 Example 26

- $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 8.11-8.08 (m, 2H), 7.68-7.66 (m, 1H), 7.58-7.54 (m, 2H), 7.38-7.34 (m, 4H), 7.16-7.13 (m, 3H), 7.00-6.98 (m, 1H), 5.55 (s, 2H), 4.36 (s, 2H), 3.64-3.58 (m, 1H), 3.31-3.30 (m, 1H), 3.05-3.04 (m, 2H), 2.85-2.81 (m, 1H), 2.55-2.53 (m,
- 25

2H), 2.05-2.01 (m, 1H), 1.80-1.75 (m, 1H), 1.58-1.52 (m, 2H), 1.24 (t,  $J = 7.3\text{Hz}$ , 3H).

MS (ESI+) 504 ( $M^+ + 1$ , 71%).

#### Example 27

5  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 8.24 (s, 1H), 7.46-7.37 (m, 2H), 7.18-7.04 (m, 6H), 4.46-4.40 (m, 2H), 4.07 (q,  $J = 7.1\text{Hz}$ , 2H), 3.73-3.65 (m, 4H), 3.34-3.33 (m, 1H), 3.12-3.08 (m, 2H), 2.81-2.80 (m, 1H), 2.00-1.99 (m, 1H), 1.70-1.69 (m, 1H), 1.59-1.50 (m, 2H), 1.10 (t,  $J =$   
10  $7.1\text{Hz}$ , 3H).

MS (ESI+) 524 ( $M^+ + 1$ , 99%).

#### Example 28

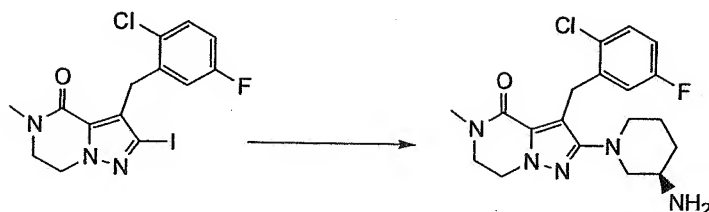
$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 8.38 (s, 1H), 8.11-8.10 (m, 1H), 8.10 (bs, 3H), 7.95-7.94 (m, 1H), 7.81 (d,  $J =$   
15  $8.3\text{Hz}$ , 1H), 7.58-7.56 (m, 2H), 7.46-7.44 (m, 1H), 7.38-7.36 (m, 1H), 7.24-7.22 (m, 2H), 7.09-7.07 (m, 1H), 6.96 (d,  $J = 6.5\text{Hz}$ , 1H), 5.93 (s, 2H), 4.37-4.35 (m, 2H), 4.05 (q,  $J = 7.0\text{Hz}$ , 2H), 3.68-3.65 (m, 1H), 3.25-3.10 (m, 2H), 3.01-2.95 (m, 1H), 2.68-2.65 (m, 1H),  
20 1.92-1.90 (m, 1H), 1.75-1.71 (m, 1H), 1.47-1.39 (m, 2H), 1.04 (t,  $J = 7.0\text{Hz}$ , 3H).

MS (ESI+) 570 ( $M^+ + 1$ , 100%).

#### Example 29

2-[(3R)-3-aminopiperidin-1-yl]-3-(2-chloro-5-  
25 fluorobenzyl)-5-methyl-6,7-dihydropyrazolo[1,5-

a]pyrazin-4(5H)-one



A suspension of 3-(2-chloro-5-fluorobenzyl)-  
 2- iodo-5-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-  
 4(5H)-one (420 mg), (R)-tert-3-butylpiperidin-3-yl  
 5 carbamate (400 mg), cesium carbonate (652 mg) and  
 copper iodide (9.5 mg) in n-butyronitrile (5 ml) was  
 stirred in a sealed tube at 110°C for 20 hours. Then,  
 copper iodide (20 mg) was added thereto, followed by  
 stirring at the same temperature for 10 hours. After  
 10 cooling to room temperature, a product (100 mg) was  
 obtained by purification by a silica gel column  
 chromatography (hexane/ethyl acetate = 1/1).  
 Subsequently, to a solution of this product in methanol  
 (4 ml) was added a 12N aqueous hydrochloric acid  
 15 solution (2 ml) at room temperature, and after standing  
 overnight, the reaction solution was concentrated under  
 reduced pressure. Water and potassium carbonate were  
 added to the residue to make the solution basic,  
 followed by two runs of extraction with chloroform.  
 20 The combined organic layer was dried over anhydrous  
 sodium sulfate and filtered, and the filtrate was  
 concentrated under reduced pressure. The residue was  
 purified by a silica gel column chromatography

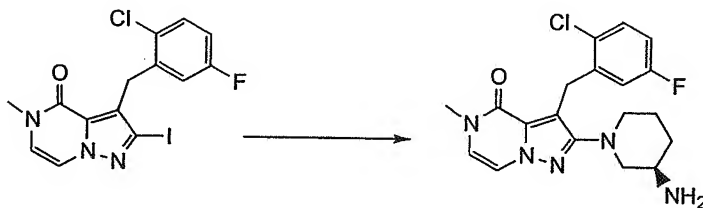
(chloroform/methanol = 10/1 ~

chloroform/methanol/triethylamine = 10/1/0.1) to obtain the title compound (1 mg).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.33-7.27 (m, 1H), 6.85-6.79 (m 1H), 6.76-6.70 (m, 1H), 4.32-4.18 (m, 4H), 3.79-3.72 (m, 2H), 3.20-3.12 (m, 1H), 3.10 (s, 3H), 3.02-2.93 (m, 1H), 2.90-2.76 (m, 1H), 2.74-2.66 (m, 1H), 2.57-2.48 (m, 1H), 2.10-1.10 (m, 4H).  
MS (ESI+) 392 (M<sup>+</sup>+1, 100%) .

#### 10 Example 30

2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chloro-5-fluorobenzyl)-5-methylpyrazolo[1,5-a]pyrazin-4(5H)-one



A suspension of 3-(2-chloro-5-fluorobenzyl)-2-iodo-5-methylpyrazolo[1,5-a]pyrazin-4(5H)-one (100 mg), (R)-tert-3-butylpiperidin-3-yl carbamate (96 mg), potassium phosphate (102 mg), ethylene glycol (30 mg) and copper iodide (2.3 mg) in 2-propanol (2 ml) was stirred in a sealed tube at 80°C for 8 hours and then at 110°C for 20 hours. After cooling to room temperature, water was added, followed by two runs of extraction with ethyl acetate. The combined organic layer was concentrated under reduced pressure. The

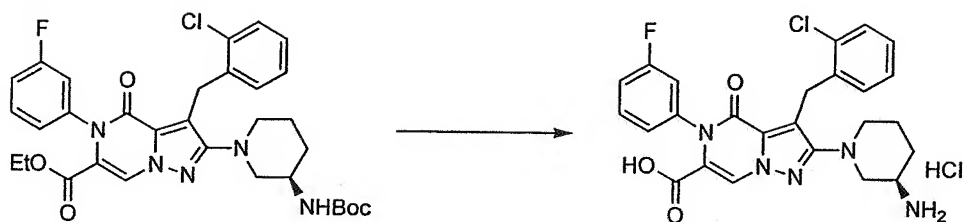
resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 1/1) to obtain a product (25 mg). Subsequently, to a solution of this product in methanol (5 ml) was added a 12N aqueous  
5 hydrochloric acid solution (2 ml) at room temperature and the resulting mixture was allowed to stand for 2 hours. The reaction mixture was concentrated under reduced pressure and 1N hydrochloric acid was added to the residue, followed by extraction with ethyl acetate.  
10 The aqueous layer was made basic with potassium carbonate and extracted twice with chloroform. The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain the title compound (2  
15 mg) as a brown solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.35-7.30 (m, 1H), 7.28 (d,  $J = 5.9\text{Hz}$ , 1H), 6.87-6.80 (m, 1H), 6.74-6.69 (m, 1H), 6.44 (d,  $J = 5.9\text{Hz}$ , 1H), 4.45 (d,  $J = 17.4\text{Hz}$ , 1H), 4.38 (d,  $J = 17.4\text{Hz}$ , 1H), 3.46 (s, 3H), 3.35-3.28 (m, 20 1H), 3.20-3.12 (m, 1H), 2.88-2.72 (m, 2H), 2.61-2.53 (m, 1H), 1.89-1.80 (m, 1H), 1.72-1.17 (m, 3H).

MS (ESI+) 390 ( $\text{M}^+ + 1$ , 100%).

#### Example 31

2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-  
25 chlorobenzyl)-5-(3-fluorophenyl)-4-oxo-4,5-  
dihydropyrazolo[1,5-a]pyrazine-6-carboxylic acid  
hydrochloride



A 1N-aqueous sodium hydroxide solution (1.0 ml) was added to a solution of ethyl 2-((3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl)-3-(2-chlorobenzyl)-5-(3-fluorophenyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazine-6-carboxylate (88.0 mg) in 1,4-dioxane (2.0 ml), and the resulting mixture was stirred at 50°C for 2 hours. After cooling to room temperature, a 5% aqueous sodium hydrogensulfate solution (20 ml) was added, followed by two runs of extraction with ethyl acetate (20 ml). The combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (silica gel, chloroform/methanol = 50/1) to obtain a purified substance (62.6 mg). A 4N hydrochloric acid/1,4-dioxane solution (1.0 ml) was added to a suspension (0.1 ml) of the purified substance (59.6 mg) in 1,4-dioxane, and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to obtain the title compound as a crude product (60.0 mg).

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 8.27 (s, 1H), 8.22-8.20 (m, 3H), 7.46-7.44 (m, 2H), 7.25-7.21 (m, 4H), 7.14-

7.12 (m, 1H), 7.04-7.03 (m, 1H), 4.31 (s, 2H), 3.67-3.66 (m, 1H), 3.30-3.28 (m, 1H), 3.15-3.13 (m, 1H), 3.02-2.99 (m, 1H), 2.68-2.65 (m, 1H), 1.93-1.91 (m, 1H), 1.68-1.66 (m, 1H), 1.50-1.38 (m, 2H).  
 5 MS (ESI+) 496 ( $M^+ + 1$ , 100%).

## Example 32

Ethyl 2-[(3R)-3-aminopiperidin-1-yl]-3-(2-chloro-5-fluorobenzyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazine-6-carboxylate methanesulfonate



10 To a solution of ethyl N-({5-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-4-(2-chloro-5-fluorobenzyl)-1-[(dimethylamino)sulfonyl]-1H-pyrazol-3-yl}carbonyl)-3-ethoxy-O-ethylserinate (300 mg) in 1,4-dioxane (4 ml) was added 4N hydrochloric acid/1,4-dioxane (8 ml), and the resulting mixture was stirred at 50°C for 1 hour. After the mixture was allowed to cool, a saturated aqueous sodium hydrogencarbonate solution was added, followed by extraction with chloroform. The organic layer was washed with a  
 15 saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered, and the filtrate was concentrated under reduced pressure. The resulting  
 20

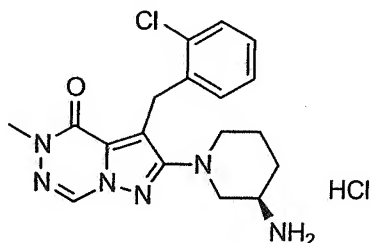
solid was dissolved in 2-propanol (20 ml), followed by adding thereto methanesulfonic acid (77 mg). The resulting mixture was stirred at 60°C for 30 minutes and allowed to cool. The solid thus obtained was collected by filtration and washed with 2-propanol to obtain the title compound (115 mg) as a white solid.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 8.18 (s, 1H), 7.47-7.43 (m, 1H), 7.01-6.96 (m, 1H), 6.80-6.75 (m, 1H), 4.50-4.38 (m, 4H), 3.74-3.65 (m, 1H), 3.20-3.05 (m, 3H), 2.90-2.80 (m, 1H), 2.71 (s, 3H), 2.08-1.98 (m, 1H), 1.81-1.72 (m, 1H), 1.63-1.50 (m, 2H), 1.41 (t, J = 7.1Hz, 3H).

MS (ESI+) 448 (M<sup>+</sup>+1, 53%).

### Example 33

2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-methylpyrazolo[1,5-d][1,2,4]triazin-4(5H)-one hydrochloride



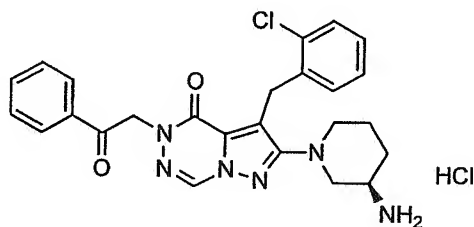
The title compound (82 mg) was synthesized by the same process as in Example 8.

<sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>) δ ppm 8.80 (s, 1H), 8.25 (bs, 3H), 7.47-7.43 (m, 1H), 7.26-7.17 (m, 2H), 7.02-6.99 (m, 1H), 4.34 (d, J=17.6Hz, 1H), 4.27 (d, J=17.6Hz,

1H), 3.49 (s, 3H), 3.47-3.45 (m, 1H), 3.13-3.09 (m, 2H), 2.96-2.89 (m, 1H), 2.62-2.58 (m, 1H), 1.92-1.88 (m, 1H), 1.63-1.60 (m, 1H), 1.46-1.32 (m, 2H).  
MS (ESI+) 373 ( $M^+ + 1$ , 43%).

# 5 Example 34

2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-(2-oxo-2-phenylethyl)pyrazolo[1,5-d][1,2,4]triazin-4(5H)-one hydrochloride



The title compound (125 mg) was synthesized  
10 by the same process as in Example 8.

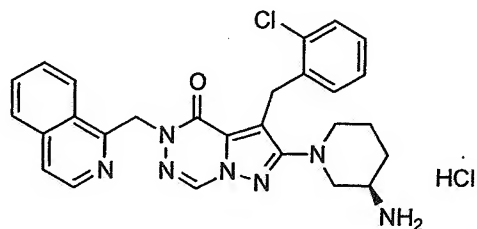
$^1\text{H}$  NMR(300MHz, DMSO- $d_6$ )  $\delta$  ppm 8.90 (s, 1H), 8.21 (bs, 3H), 8.03 (d,  $J=7.3\text{Hz}$ , 2H), 7.73-7.68 (m, 1H), 7.59-7.54 (m, 2H), 7.46-7.43 (m, 1H), 7.24-7.21 (m, 2H), 7.03-7.01 (m, 1H), 5.55 (s, 2H), 4.36 (d,  $J=17.7\text{Hz}$ , 1H), 4.29 (d,  $J=17.7\text{Hz}$ , 1H), 3.46-3.44 (m, 1H), 3.16-3.12 (m, 2H), 2.99-2.92 (m, 1H), 2.67-2.63 (m, 1H), 1.93-1.90 (m, 1H), 1.65-1.62 (m, 1H), 1.48-1.34 (m, 2H).  
15

MS (ESI+) 477 ( $M^+ + 1$ , 100%).

# 20 Example 35

2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-

chlorobenzyl)-5-(isoquinolin-1-ylmethyl)pyrazolo[1,5-d][1,2,4]triazin-4(5H)-one hydrochloride

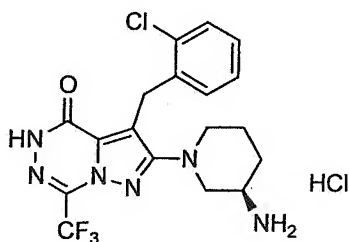


The title compound (141 mg) was synthesized by the same process as in Example 8.

- 5  $^1\text{H}$  NMR(300MHz, DMSO- $d_6$ )  $\delta$  ppm 8.89 (s, 1H), 8.50-8.48 (m, 2H), 8.39 (bs, 3H), 8.24-8.21 (m, 2H), 8.08-8.02 (m, 1H), 7.92-7.89 (m, 1H), 7.45-7.42 (m, 1H), 7.24-7.21 (m, 2H), 7.14-7.11 (m, 1H), 6.02 (s, 2H), 4.38-4.26 (m, 2H), 3.73-3.71 (m, 1H), 3.15-3.13 (m, 2H),  
 10 3.00-2.95 (m, 1H), 2.64-2.60 (m, 1H), 1.94-1.90 (m, 1H), 1.65-1.61 (m, 1H), 1.53-1.25 (m, 2H).  
 MS (ESI+) 500 ( $M^+ + 1$ , 100%).

#### Example 36

2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-7-(trifluoromethyl)pyrazolo[1,5-d][1,2,4]triazin-4(5H)-one hydrochloride



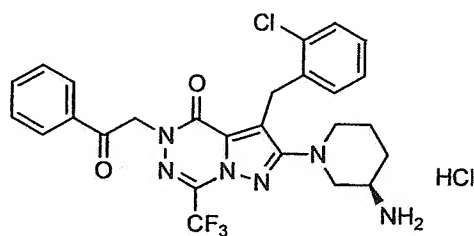
The title compound (6 mg) was synthesized by

the same process as in Example 8.

$^1\text{H}$  NMR(300MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 7.35-7.31 (m, 1H), 7.13-7.09 (m, 2H), 6.96-6.92 (m, 1H), 4.45-4.29 (m, 2H), 3.50-3.46 (m, 1H), 3.25-3.11 (m, 2H), 3.02-2.95 (m, 1H),  
 5 2.76-2.67 (m, 1H), 1.95-1.90 (m, 1H), 1.64-1.30 (m, 3H).  
 MS (ESI+) 527 ( $\text{M}^++1$ , 51%).

### Example 37

2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-(2-oxo-2-phenylethyl)-7-(trifluoromethyl)pyrazolo[1,5-d][1,2,4]triazin-4(5H)-  
 10 one hydrochloride

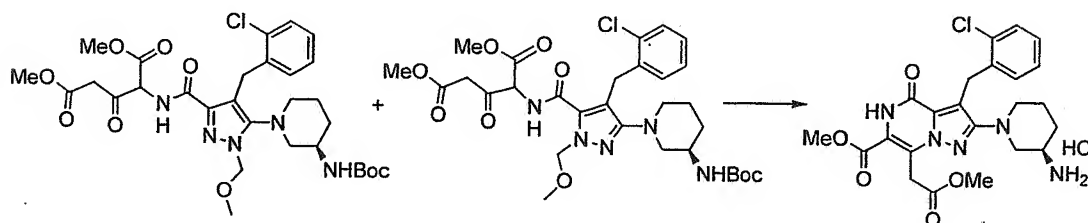


The title compound (18 mg) was synthesized by the same process as in Example 8.

$^1\text{H}$  NMR(300MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 8.08-8.02 (m, 2H), 7.71-7.61 (m, 1H), 7.53-7.48 (m, 2H), 7.38-7.33 (m, 1H), 7.12-6.98 (m, 2H), 6.86-6.83 (m, 1H), 5.84-5.69 (m, 2H),  
 15 4.35-4.24 (m, 2H), 3.62-3.44 (m, 1H), 2.97-2.70 (m, 4H), 1.92-1.81 (m, 1H), 1.64-1.60 (m, 1H), 1.46-1.21 (m, 2H).  
 20 MS (ESI+) 545 ( $\text{M}^++1$ , 85%).

### Example 38

Methyl 2-[(3R)-3-aminopiperidin-1-yl]-3-(2-chlorobenzyl)-7-(2-methoxy-2-oxoethyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazine-6-carboxylate hydrochloride



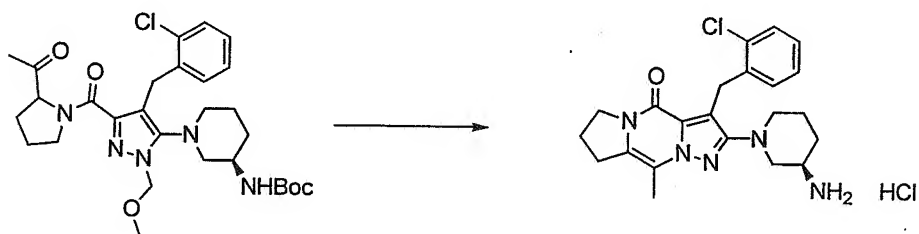
5           A dimethyl N-[[5-{(3R)-3-[(tert-butoxy-carbonyl)aminopiperidin-1-yl]-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazol-3-yl]carbonyl}-3-oxoglutamate mixture (57.5 mg) was dissolved in a 4N  
10 followed by adding thereto water (0.5 ml), and the resulting mixture was stirred at 50°C for 2 hours. The reaction solution was concentrated under reduced pressure and the water remaining in the resulting residue was distilled off as an azeotrope with methanol  
15 to obtain the title compound (40.4 mg).

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 11.05 (bs, 1H), 8.16 (bs, 3H), 7.50-7.35 (m, 1H), 7.30-7.10 (m, 2H), 7.00-6.90 (m, 1H), 4.40 (s, 2H), 4.35 (s, 2H), 3.81 (s, 3H), 3.80-3.60 (m, 1H), 3.68 (s, 3H), 3.20-2.80 (m, 4H),  
20 1.95-1.75 (m, 1H), 1.70-1.55 (m, 1H), 1.55-1.20 (m, 2H).

MS (ESI+) 488 (M<sup>+</sup>+1, 100%).

## Example 39

2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-9-methyl-7,8-dihydro-4H,6H-pyrazolo[1,5-a]pyrrolo[1,2-d]pyrazin-4-one hydrochloride

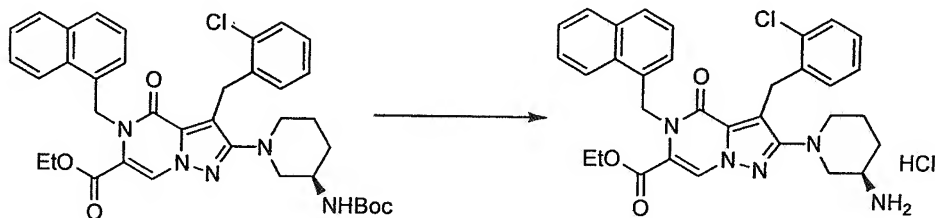


5 The title compound (15 mg) was synthesized by the same process as in Example 2.

$^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ )  $\delta$  ppm 11.05 (bs, 1H), 8.16 (bs, 3H), 7.50-7.35 (m, 1H), 7.30-7.10 (m, 2H), 7.00-6.90 (m, 1H), 4.40 (s, 2H), 4.35 (s, 2H), 3.81 (s, 3H), 3.80-3.60 (m, 1H), 3.68 (s, 3H), 3.20-2.80 (m, 4H), 1.95-1.75 (m, 1H), 1.70-1.55 (m, 1H), 1.55-1.20 (m, 2H).

MS (ESI+) 488 ( $\text{M}^++1$ , 100%).

## Example 40



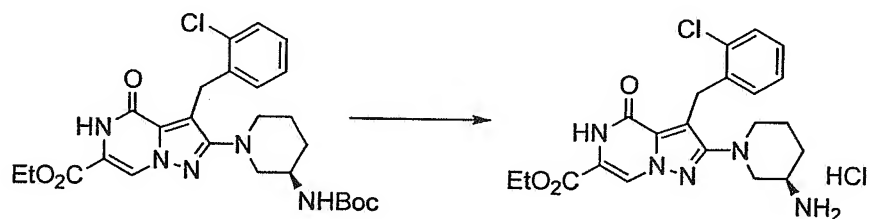
15 The title compound (127 mg) was synthesized by the same process as in Example 8.

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  ppm 8.30 (s, 1H), 8.18-8.14

(m, 4H), 7.97-7.94 (m, 1H), 7.80 (d,  $J = 8.2\text{Hz}$ , 1H), 7.58-7.55 (m, 2H), 7.45-7.42 (m, 1H), 7.37-7.36 (m, 1H), 7.23-7.21 (m, 2H), 7.05-7.03 (m, 1H), 6.92-6.90 (m, 1H), 6.03 (s, 2H), 4.34-4.31 (m, 2H), 3.68-3.64 (m, 1H), 3.19-3.17 (m, 1H), 3.08-3.06 (m, 1H), 3.00-2.95 (m, 1H), 2.67-2.65 (m, 1H), 1.93-1.91 (m, 1H), 1.67-1.65 (m, 1H), 1.50-1.40 (m, 2H).  
 MS (ESI+) 542 ( $M^+ + 1$ , 76%).

## Example 41

10 Ethyl 2-[(3R)-3-aminopiperidin-1-yl]-3-(2-chlorobenzyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazine-6-carboxylate hydrochloride

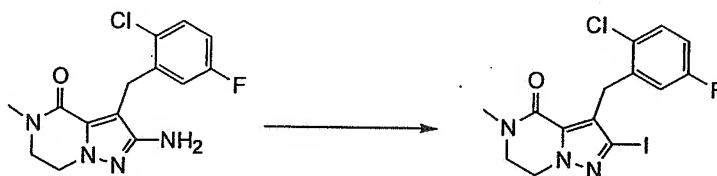


The title compound (23 mg) was synthesized by the same process as in Example 8.

15  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ) 8.16 (s, 1H), 8.05-8.00 (m, 4H), 7.47-7.45 (m, 1H), 7.26-7.18 (m, 2H), 7.00-6.97 (m, 1H), 4.38-4.27 (m, 4H), 3.59-3.57 (m, 1H), 3.18-3.16 (m, 1H), 3.05-3.02 (m, 1H), 2.95-2.92 (m, 1H), 2.61-2.52 (m, 1H), 1.91-1.90 (m, 1H), 1.72-1.69 (m, 1H), 1.43-1.37 (m, 2H), 1.31 (t,  $J = 7.1\text{Hz}$ , 3H).  
 20 MS (ESI+) 430 ( $M^+ + 1$ , 50%).

## Reference Example 1

3-(2-Chloro-5-fluorobenzyl)-2-iodo-5-methyl-  
6,7- dihydropyrazolo[1,5-a]pyrazin-4(5H)-one



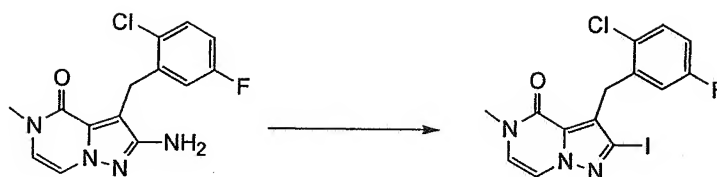
To a mixture of diiodomethane (5 ml) and  
5 isoamyl nitrite (2.2 ml) was added 2-amino-3-(2-chloro-  
5-fluorobenzyl)-5-methyl-6,7-dihydropyrazolo[1,5-  
a]pyrazin-4(5H)-one (1 g) at room temperature, and the  
resulting mixture was stirred at the same temperature  
for 1 hour. The reaction solution was purified by a  
10 silica gel column chromatography (hexane/ethyl acetate  
= 1/1) to obtain the title compound (0.98 g) as a  
yellow solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.28-7.23 (m, 1H), 6.79-  
6.72 (m, 1H), 6.47-6.42 (m, 1H), 4.42-4.37 (m, 2H),  
15 4.11 (s, 2H), 3.73-3.68 (m, 2H), 3.04 (s, 3H).

MS (ESI+) 420 (M<sup>+</sup>+1, 100%).

## Reference Example 2

3-(2-Chloro-5-fluorobenzyl)-2-iodo-5-  
methylpyrazolo[1,5-a]pyrazin-4(5H)-one



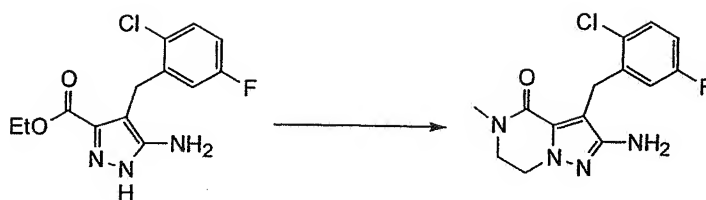
To a mixed solution of diiodomethane (5 ml) and isoamyl nitrite (2.2 ml) was added 2-amino-3-(2-chloro-5-fluorobenzyl)-5-methylpyrazolo[1,5-a]pyrazin-4(5H)-one (1 g) at room temperature, and the resulting mixture was stirred at the same temperature for 4 hours. The reaction solution was purified by a silica gel column chromatography (from chloroform to hexane/ethyl acetate = 2/1 ~ 1/1). The resulting purified substance was filtered and washed with ethyl acetate/hexane (about 1/3) and the precipitate on a filter was dried to obtain the title compound (0.77 g) as a yellow solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.44 (d,  $J = 6.0\text{Hz}$ , 1H), 7.37-7.32 (m, 1H), 6.88-6.81 (m, 1H), 6.56 (d,  $J = 6.0\text{Hz}$ , 1H), 6.51-6.46 (m, 1H), 4.34 (s, 2H), 3.49 (s, 3H).

MS (ESI+) 418 ( $\text{M}^+ + 1$ , 100%).

### Reference Example 3

2-Amino-3-(2-chloro-5-fluorobenzyl)-5-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one



Di-tert-butyl dicarbonate (70.3 g) was added to a solution of ethyl 3-amino-4-(2-chloro-5-fluorobenzyl)-1H-pyrazole-5-carboxylate (24.0 g), 4-(dimethylamino)pyridine (9.8 g) and triethylamine (56.1 ml) in tetrahydrofuran (200 ml) under ice-cooling, and the resulting mixture was stirred at the same temperature for 2 hours and then allowed to stand overnight at room temperature. Water was added thereto, followed by extraction with ethyl acetate.

10 The organic layer was washed three times with a 5% aqueous potassium hydrogensulfate solution and then with a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution, and dried over sodium sulfate. The dried

15 organic layer was filtered and the filtrate was concentrated under reduced pressure to obtain a product (60.5 g). Then, to a solution of this product in methanol (200 ml) was added a solution of sodium hydroxide (12.9 g) in water (100 ml), and the resulting

20 mixture was stirred at 50°C for 6 hours and then allowed to stand overnight at room temperature. The solvent was concentrated under reduced pressure and the residue was acidified with a 5% aqueous potassium hydrogensulfate solution (1000 ml) and extracted twice

with ethyl acetate (400 ml). The combined organic layer was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and then filtered, and the filtrate was concentrated under reduced pressure to obtain a product (35.7 g). To a solution of this product (17.9 g) in N,N-dimethylformamide (100 ml) were added 1-hydroxybenzotriazole (6.16 g) and N-methylaminoethanol (3.03 g), followed by adding thereto 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (7.72 g) under ice-cooling, and the resulting mixture was stirred at the same temperature for 1 hour and allowed to stand overnight at room temperature. Ice water (500 ml) was added to the reaction mixture and the crystals precipitated were filtered. This solid was dissolved in methanol/chloroform (about 1/1) and the resulting solution was concentrated under reduced pressure. Ethanol/toluene (about 1/1) was added to the concentrate and the resulting mixture was concentrated under reduced pressure to obtain the residue. The aqueous layer of the filtrate was extracted with ethyl acetate (500 ml) and the extract solution was washed with a saturated aqueous sodium chloride solution (300 ml), dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure to obtain the residue. These residues were combined to obtain a product (24.8 g). To a solution of this product in N,N-dimethylformamide (100 ml) was added

triphenylphosphine (15.8 g), followed by adding thereto carbon tetrabromide (20 g) under ice-cooling, and the resulting mixture was stirred at the same temperature for 15 minutes and then at room temperature for 1 hour.

5 Potassium carbonate (16.7 g) was added to the reaction solution, followed by stirring at 70°C for 2 hours. The resulting mixture was cooled to room temperature, poured into ice water (500 ml) and then extracted twice with ethyl acetate (300 ml). The combined organic

10 layer was washed twice with water (300 ml) and then once with a saturated aqueous sodium chloride solution, and concentrated under reduced pressure to obtain a product (48 g). To a solution of this product in methanol (200 ml) was added a 12N aqueous hydrochloric

15 acid solution (100 ml) and the resulting mixture was allowed to stand overnight at room temperature. After the solvent was concentrated under reduced pressure, a 3N aqueous hydrochloric acid solution (200 ml) and water (300 ml) were added, and the resulting mixture

20 was washed with ethyl acetate (500 ml). The aqueous layer was made basic with potassium carbonate and extracted twice with chloroform (300 ml). The combined organic layer was washed with a saturated aqueous sodium chloride solution, dried over sodium sulfate and

25 then filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (from chloroform/ethyl acetate = 2/3 to ethyl acetate, ethyl

acetate/methanol = 10/1). The resulting purified substance was filtered and washed with toluene/hexane (about 1/2) and dried to obtain the title compound (3.9 g) as a white solid.

- 5  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.32-7.28 (m, 1H), 6.98-6.93 (m, 1H), 6.86-6.81 (m, 1H), 4.20 (s, 2H), 4.22-4.18 (m, 2H), 3.75-3.71 (m, 2H), 3.62 (s, 2H), 3.11 (s, 3H).

#### Reference Example 4

- 10 2-Amino-3-(2-chloro-5-fluorobenzyl)-5-methylpyrazolo[1,5-a]pyrazin-4(5H)-one



- Di-tert-butyl dicarbonate (70.3 g) was added to a solution of ethyl 3-amino-4-(2-chloro-5-fluorobenzyl)-1H-pyrazole-5-carboxylate (24.0 g),
- 15 dimethylaminopyridine (9.8 g) and triethylamine (56.1 ml) in tetrahydrofuran (200 ml) under ice-cooling, and the resulting mixture was stirred at the same temperature for 2 hours and then allowed to stand overnight at room temperature. Water was added
- 20 thereto, followed by extraction with ethyl acetate, and the organic layer was washed three times with a 5% aqueous potassium hydrogensulfate solution and then

with a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure to obtain a product (60.5 g). Subsequently, to a solution of this product in methanol (200 ml) was added a solution of sodium hydroxide (12.9 g) in water (100 ml), and the resulting mixture was stirred at 50°C for 6 hours and then allowed to stand overnight at room temperature. The solution thus obtained was concentrated under reduced pressure, acidified with a 5% aqueous potassium hydrogensulfate solution (1000 ml), and then extracted twice with ethyl acetate (400 ml). The combined organic layer was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and then filtered, and the filtrate was concentrated under reduced pressure to obtain a product (35.7 g). To a solution of this product (17.9 g) in N,N-dimethylformamide (100 ml) were added 1-hydroxybenzotriazole (6.16 g) and N-methylacetaldehyde dimethylacetal (4.8 g), followed by adding thereto 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (7.72 g) under ice-cooling, and the resulting mixture was stirred at the same temperature for 1 hour and allowed to stand overnight at room temperature. Ice water was added to the reaction mixture, followed by two runs of extraction with ethyl acetate. The combined organic layer was washed twice

with a 5% aqueous potassium hydrogensulfate solution and then successively with a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. To a solution of the resulting residue in 1,4-dioxane (50 ml) was added 4N hydrochloric acid/1,4-dioxane (100 ml) at room temperature and the resulting mixture was allowed to stand at the same temperature for 5 hours.

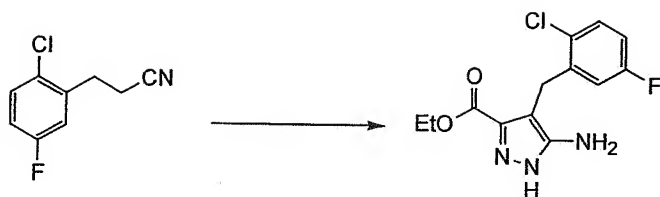
Toluene/hexane was added to the reaction solution and the solid precipitated was filtered. The solid thus obtained was dissolved in water and the resulting solution was made basic with a saturated aqueous sodium hydrogencarbonate solution and extracted twice with chloroform. The combined organic layer was concentrated under reduced pressure. The residue was washed with chloroform and dried to obtain the title compound (4.1 g) as a white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.34-7.30 (m, 1H), 7.19 (d,  $J = 5.9\text{Hz}$ , 1H), 7.00-6.95 (m, 1H), 6.88-6.82 (m, 1H), 6.41 (d,  $J = 5.9\text{Hz}$ , 1H), 4.35 (s, 2H), 3.86 (s, 2H), 3.49 (s, 3H).

MS (ESI+) 307 ( $\text{M}^+ + 1$ , 100%).

## Reference Example 5

Ethyl 3-amino-4-(2-chloro-5-fluorobenzyl)-1H-pyrazole-5-carboxylate



Sodium (3.7 g) was added to ethanol (100 ml) in small portions under ice-cooling and stirred until it was completely dissolved. A solution of 3-(2-chloro-5-fluorophenyl)propanenitrile (24.0 g) and

5 diethyl oxalate (16.8 ml) in ethanol (50 ml) was added dropwise thereto, and the resulting mixture was stirred at 80°C for 6 hours and allowed to stand overnight. Ice water was added thereto and the pH was adjusted to 1 with a 1N aqueous hydrochloric acid solution,

10 followed by two runs of extraction with ethyl acetate. The combined organic layer was washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and then filtered, and the filtrate was concentrated under reduced pressure to obtain a product

15 (36.1 g). Subsequently, to a suspension of this product in ethanol (150 ml) were added hydrazine hydrate (9 ml) and acetic acid (20 ml), and the resulting mixture was stirred at 80°C for 3 hours. The reaction solution was cooled to room temperature and

20 ice water was added thereto. Then, the resulting mixture was made basic with a 5% aqueous potassium carbonate solution and the insoluble material precipitated was filtered. The insoluble material was

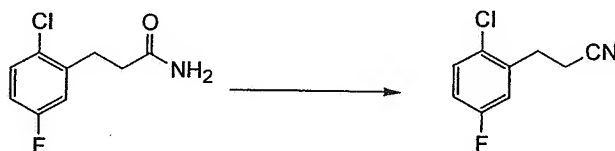
dissolved in methanol, followed by adding thereto toluene, and the resulting mixture was concentrated under reduced pressure. The solid precipitated was washed with hexane/toluene and dried to obtain the  
 5 title compound (24.0 g) as a white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.35-7.31 (m, 1H), 6.88-6.83 (m, 1H), 6.77-6.73 (m, 1H), 4.30 (q,  $J = 7.1\text{Hz}$ , 2H), 4.08 (s, 2H), 1.23 (t,  $J = 7.1\text{Hz}$ , 3H).

MS (ESI+) 298 ( $\text{M}^+ + 1$ , 100%).

#### 10 Reference Example 6

##### 3-(2-Chloro-5-fluorophenyl)propanenitrile



Phosphorus oxychloride (23.66 g) was added to a suspension of 3-(2-chloro-5-fluorophenyl)propanamide (24.9 g) in toluene (200 ml) at room temperature, and  
 15 the resulting mixture was stirred at  $80^\circ\text{C}$  for 6 hours. The reaction solution was cooled to room temperature and ice water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed successively with water, a saturated aqueous sodium  
 20 hydrogencarbonate solution and a saturated aqueous sodium chloride solution, dried over magnesium sulfate and then filtered, and the filtrate was concentrated under reduced pressure to obtain the title compound

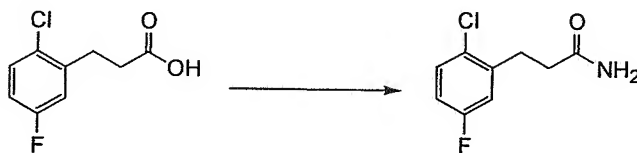
(24.0 g) as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.37-7.33 (m, 1H), 7.07-7.02 (m, 1H), 7.00-6.94 (m, 1H), 3.06 (t,  $J = 7.3\text{Hz}$ , 2H), 2.69 (t,  $J = 7.3\text{Hz}$ , 2H).

5 MS (ESI+) 184 ( $\text{M}^+ + 1$ , 100%).

#### Reference Example 7

##### 3-(2-Chloro-5-fluorophenyl)propanamide



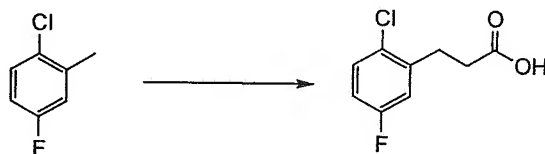
Thionyl chloride (15 ml) was added dropwise to a solution of 3-(2-chloro-5-fluorophenyl)propionic acid (38.8 g) and N,N-dimethylformamide (0.1 ml) in toluene (400 ml) at room temperature, and the resulting mixture was stirred at 60°C for 3 hours. The solvent was concentrated under reduced pressure and toluene (200 ml) was added, followed by concentration under reduced pressure. Toluene (50 ml) was added to the residue to obtain a solution. This solution was added dropwise to 28% aqueous ammonia (233 ml) under ice-cooling and the resulting mixture was stirred at the same temperature for 30 minutes and then at room temperature for 6 hours, and allowed to stand overnight at the same temperature. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The combined organic layer was washed with a

1N aqueous hydrochloric acid solution, a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution, dried over magnesium sulfate and then filtered, and the filtrate  
 5 was concentrated under reduced pressure. The solid precipitated was washed with hexane/ethyl acetate and dried to obtain the title compound (23.6 g) as a white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.33-7.28 (m, 1H), 7.04-  
 10 6.99 (m, 1H), 6.92-6.85 (m, 1H), 5.52 (d,  $J = 6.4\text{Hz}$ , 2H), 3.06 (t,  $J = 7.7\text{Hz}$ , 2H), 2.54 (t,  $J = 7.7\text{Hz}$ , 2H).  
 MS (ESI+) 202 ( $\text{M}^+ + 1$ , 100%).

#### Reference Example 8

##### 3-(2-Chloro-5-fluorophenyl)propionic acid



15 To a solution of 2-chloro-5-fluorotoluene (50.0 g) in carbon tetrachloride (750 ml) were added N-bromosuccinimide (67.7 g) and azoisobutyronitrile (0.7 g), and the resulting mixture was stirred with heating under reflux for 3 hours and allowed to stand overnight  
 20 at room temperature. The insoluble material precipitated was filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column

chromatography (hexane/ethyl acetate = 1/1) to obtain a purified substance (82.2 g). A solution (150 ml) of this product in dimethyl sulfoxide was added dropwise to a solution of meldramic acid (150 g) and

5 triethylamine (100 ml) in dimethyl sulfoxide (500 ml) under ice-cooling over a period of 30 minutes, and the resulting mixture was allowed to stand at room temperature for 3 days. The reaction solution was poured into ice water (2000 ml) and extracted twice

10 with ethyl acetate (1000 ml), and the combined organic layer was concentrated under reduced pressure to obtain a product. Then, a suspension of this product in methanol (600 ml) was stirred with heating under reflux for 10 hours and allowed to stand overnight at room

15 temperature. The reaction mixture was concentrated under reduced pressure and water (500 ml) was added thereto, followed by two runs of extraction with ethyl acetate (300 ml). The combined organic layer was concentrated under reduced pressure to obtain a product

20 (110 g). Subsequently, to this product were added 1,4-dioxane (500 ml) and a 12N aqueous hydrochloric acid solution (200 ml), and the resulting mixture was stirred with heating under reflux for 20 hours. The mixture was cooled to room temperature and then

25 concentrated under reduced pressure and water (500 ml) was added thereto, followed by two runs of extraction with ethyl acetate (500 ml). The combined organic layer was concentrated under reduced pressure, followed

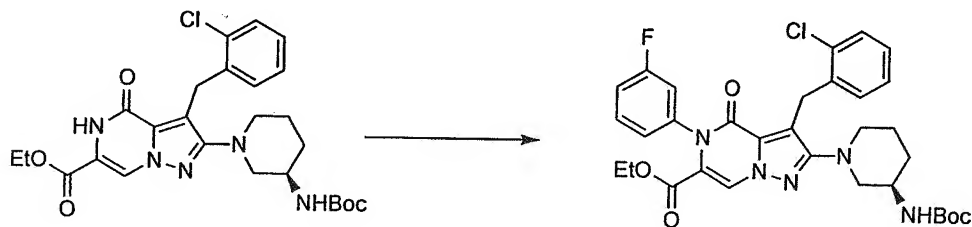
by adding thereto a solution of potassium carbonate (70 g) in water (500 ml) and a solution of sodium hydroxide (40 g) in water (300 ml), and the resulting mixture was washed with hexane (500 ml). The aqueous layer was acidified with 12N hydrochloric acid and extracted three times with chloroform (1000 ml). After the combined organic layer was concentrated under reduced pressure, tetrahydrofuran was added to the residue and the insoluble material was filtered off. The filtrate was concentrated under reduced pressure to obtain the title compound (38.8 g).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.33-7.29 (m, 1H), 7.02-6.98 (m, 1H), 6.93-6.87 (m, 1H), 3.04 (t,  $J = 7.7\text{Hz}$ , 2H), 2.71 (t,  $J = 7.7\text{Hz}$ , 2H).

MS (ESI+) 203 ( $\text{M}^+ + 1$ , 100%).

#### Reference Example 9

Ethyl 2-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-3-(2-chlorobenzyl)-5-(3-fluorophenyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazine-6-carboxylate



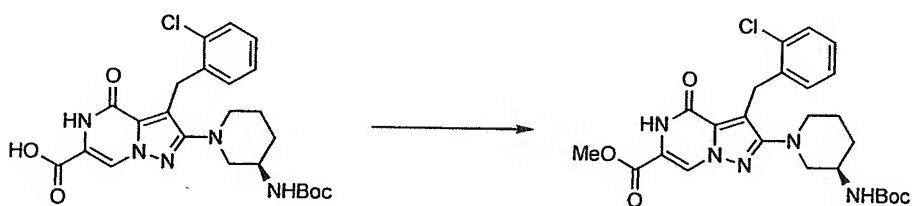
To a solution of ethyl 2-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-3-(2-chlorobenzyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazine-

6-carboxylate (100 mg) in dichloromethane (1.5 ml) were added 3-fluorophenylboric acid (79.3 mg), copper(II) acetate (68.5 mg), molecular sieves (4Å, 80 mg) and pyridine (0.0611 ml), and the resulting mixture was stirred overnight at room temperature. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 3/1) to obtain the title compound (90.0 mg).

MS (ESI+) 624 ( $M^+ + 1$ , 92%).

## Reference Example 10

Methyl 2-((3R)-3-((tert-butoxycarbonyl)amino)piperidin-1-yl)-3-(2-chlorobenzyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazine-6-carboxylate



Methanol (0.072 ml), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (343 mg), 1-hydroxybenzotriazole monohydrate (242 mg) and triethylamine (0.248 ml) were added to a solution of 2-((3R)-3-((tert-butoxycarbonyl)amino)piperidin-1-yl)-3-(2-chlorobenzyl)-4-oxo-4,5-dihydropyrazolo[1,5-

alpyrazine-6-carboxylic acid (448 mg) in N,N-dimethylformamide (20 ml), and the resulting mixture was stirred overnight at room temperature. A saturated aqueous sodium hydrogencarbonate solution (200 ml) was added thereto, followed by two runs of extraction with ethyl acetate (100 ml), and the combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 2/1) to obtain the title compound (255 mg).  
 MS (ESI+) 516 ( $M^+ + 1$ , 35%).

## Reference Example 11

2-((3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl)-3-(2-chlorobenzyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazine-6-carboxylic acid

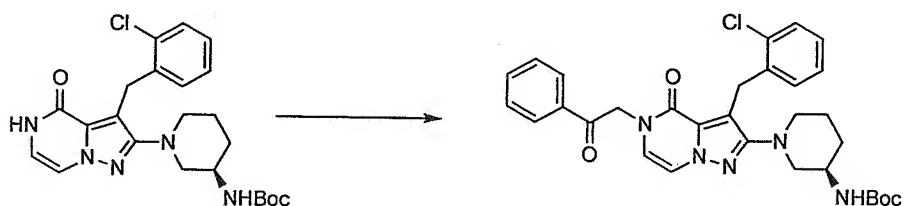


A 1N-aqueous sodium hydroxide solution (10 ml) was added to a solution of ethyl 2-((3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl)-3-(2-chlorobenzyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazine-6-carboxylate (1.00 g) in 1,4-dioxane (10 ml), and the resulting mixture was stirred at 50°C for 2 hours. The

mixture was cooled to room temperature and a 5% aqueous sodium hydrogensulfate solution (20 ml) was added thereto, followed by two runs of extraction with ethyl acetate (20 ml). The combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (chloroform/methanol = 10/1) to obtain the title compound (872 mg).  
 MS (ESI+) 502 ( $M^+ + 1$ , 66%).

# 10 Reference Example 12

tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydropyrazolo[1,5-a]pyrazin-2-yl]piperidin-3-yl}carbamate

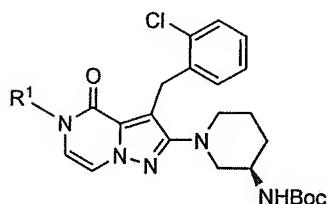


Phenacyl bromide (59.7 mg) and potassium carbonate (82.8 mg) were added to a solution of tert-butyl {(3R)-1-[3-(2-chlorobenzyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-2-yl]piperidin-3-yl}carbamate (91.6 mg) in N,N-dimethylformamide (1.0 ml), and the resulting mixture was stirred overnight at room temperature. Water (20 ml) was added to the reaction mixture, followed by two runs of extraction with ethyl acetate (20 ml), and the combined organic

layer was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 2/1) to obtain the title compound (38.8 mg).

5 MS (ESI+) 576 ( $M^+ + 1$ , 100%).

The following compounds of Reference Examples 12-1 to 12-8 were synthesized by the same process as above.



Reference example number	R <sup>1</sup>	Reference example number	R <sup>1</sup>
Reference Example 12-1		Reference Example 12-5	
Reference Example 12-2		Reference Example 12-6	
Reference Example 12-13		Reference Example 12-7	
Reference Example 12-4			

## Reference Example 12-1

MS (ESI+) 606 ( $M^+ + 1$ , 100%).

## Reference Example 12-2

MS (ESI+) 634 ( $M^+ + 1$ , 100%).

## 5 Reference Example 12-3

MS (ESI+) 599 ( $M^+ + 1$ , 100%).

## Reference Example 12-4

MS (ESI+) 573 ( $M^+ + 1$ , 100%).

## Reference Example 12-5

10 MS (ESI+) 606 ( $M^+ + 1$ , 100%).

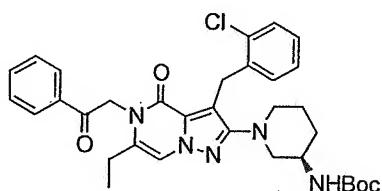
## Reference Example 12-6

MS (ESI+) 562 ( $M^+ + 1$ , 100%).

## Reference Example 12-7

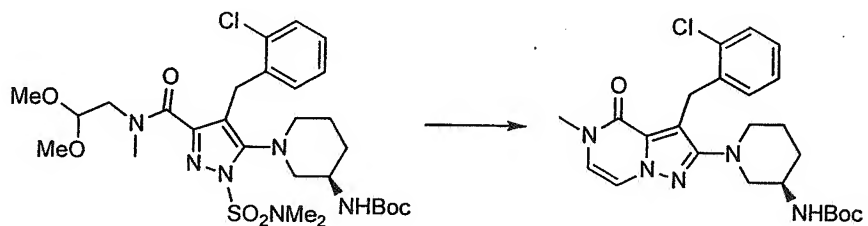
MS (ESI+) 530 ( $M^+ + 1$ , 59%).

## 15 Reference Example 12-8

MS (ESI+) 604 ( $M^+ + 1$ , 100%).

## Reference Example 13

tert-Butyl ((3R)-1-[3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-2-yl]piperidin-3-yl)carbamate



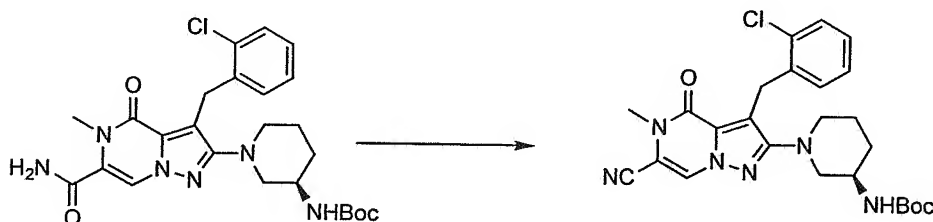
- 5 Water (4.0 ml) and a 4N hydrochloric acid/1,4-dioxane solution (8.0 ml) were added to a solution of tert-butyl ((3R)-1-[4-(2-chlorobenzyl)-3-  
 10 {[(2,2-dimethoxyethyl)(methyl)-amino]carbonyl}-1-[(dimethylamino)sulfonyl]-1H-pyrazol-5-yl]piperidin-3-yl)carbamate (386 mg) in 1,4-dioxane (4.0 ml), and the resulting mixture was stirred at 50°C for 2 hours. A 5% aqueous potassium carbonate solution (100 ml) was added to the reaction mixture, followed by two runs of extraction with chloroform (100 ml), and the combined  
 15 organic layer was concentrated under reduced pressure. To a solution of the resulting residue in 1,4-dioxane (1.0 ml) were added sodium hydrogencarbonate (168.0 mg) and di-tert-butyl dicarbonate (328 mg), and stirred overnight. Water (100 ml) was added to the reaction  
 20 mixture, followed by two runs of extraction with ethyl acetate (100 ml), and the combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a silica gel column

chromatography (hexane/ethyl acetate = 1/1) to obtain the title compound (16.5 mg).

MS (ESI+) 472 ( $M^+ + 1$ , 49%).

#### Reference Example 14

- 5                   tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-6-cyano-5-methyl-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-2-yl]piperidin-3-yl}carbamate



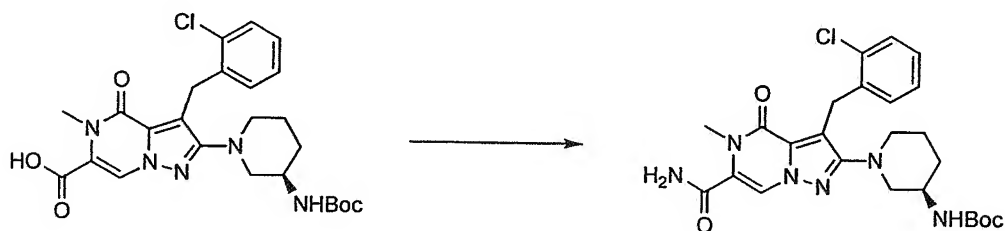
- Trifluoroacetic anhydride (0.18 ml) was added to a solution of tert-butyl {(3R)-1-[6-(aminocarbonyl)-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-2-yl]piperidin-3-yl}carbamate (120 mg) in tetrahydrofuran (3.0 ml), and the resulting mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in methanol (2.5 ml). Water (0.05 ml) and potassium carbonate (48.3 mg) were added thereto and the resulting mixture was stirred at room temperature for 1 hour. Water (50 ml) was added to the reaction mixture, followed by two runs of extraction with ethyl acetate (50 ml), and the combined organic layer was concentrated under reduced pressure. The resulting
- 10
- 15
- 20

residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 2/1) to obtain the title compound (68.5 mg).

MS (ESI+) 497 ( $M^+ + 1$ , 67%).

## 5 Reference Example 15

tert-Butyl {(3R)-1-[6-(aminocarbonyl)-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-2-yl]piperidin-3-yl}carbamate



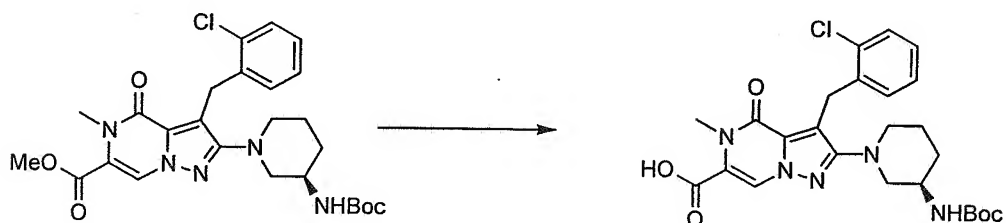
Ammonium chloride (106 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (380 mg), 1-hydroxybenzotriazole monohydrate (268 mg) and triethylamine (0.551 m) were added to a solution of 2-((3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl)-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-6-carboxylic acid (340 mg) in dimethylformamide (6.0 ml), and the resulting mixture was stirred overnight at room temperature. A saturated aqueous sodium hydrogencarbonate solution (200 ml) was added thereto, followed by two runs of extraction with ethyl acetate (100 ml), and the combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a

silica gel column chromatography (hexane/ethyl acetate = 1/2) to obtain the title compound (236 mg).

MS (ESI+) 515 ( $M^+ + 1$ , 72%).

# Reference Example 16

5                    2-((3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl)-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydropyrazolo[1,5-  
alpyrazin-6-carboxylic acid



A 1N-aqueous sodium hydroxide solution (4.0  
10 ml) was added to a solution of methyl 2-((3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl)-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydropyrazolo[1,5-  
alpyrazin-6-carboxylate (340 mg) in 1,4-dioxane (4.0 ml), and the resulting mixture was stirred at 50°C for  
15 2 hours. After cooling to room temperature, a 5% aqueous sodium hydrogensulfate solution (50 ml) was added, followed by two runs of extraction with ethyl acetate (50 ml), and the combined organic layer was concentrated under reduced pressure to obtain the title  
20 compound as a crude product (340 mg).

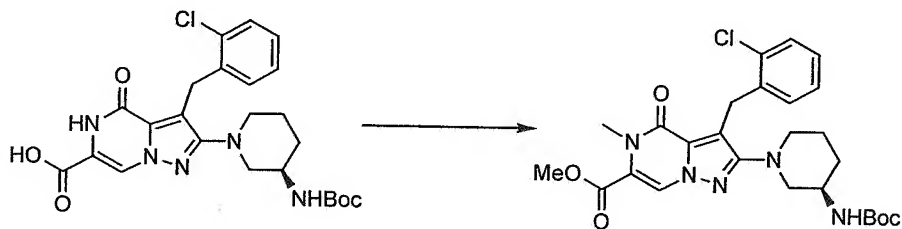
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 8.27 (s, 1H), 7.40-7.37 (m, 1H), 7.16-7.12 (m, 2H), 6.96-6.93 (m, 1H), 4.70-

4.68 (m, 1H), 4.64-4.41 (m, 2H), 3.76-3.72 (m, 1H),  
 3.71 (s, 3H), 3.33-3.29 (m, 1H), 3.03-3.00 (m, 2H),  
 2.91-2.89 (m, 1H), 1.67-1.65 (m, 2H), 1.50-1.45 (m,  
 2H), 1.45 (s, 9H).

5 MS (ESI+) 516 ( $M^+ + 1$ , 73%).

#### Reference Example 17

Methyl 2-((3R)-3-[(tert-  
 butoxycarbonyl)amino]piperidin-1-yl)-3-(2-  
 chlorobenzyl)-5-methyl-4-oxo-4,5-dihydropyrazolo[1,5-  
 10 a]pyrazin-6-carboxylate



Methyl iodide (0.097 ml) and potassium  
 carbonate (495 mg) were added to a solution of 2-((3R)-  
 3-[(tert-butoxycarbonyl)amino]piperidin-1-yl)-3-(2-  
 chlorobenzyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-  
 15 6-carboxylic acid (490 mg) in N,N-dimethylformamide (10  
 ml), and the resulting mixture was stirred at room  
 temperature for 6 hours. Water (100 ml) was added to  
 the reaction mixture, followed by two runs of  
 extraction with ethyl acetate (100 ml), and the  
 20 combined organic layer was concentrated under reduced  
 pressure to obtain the title compound as a crude  
 product (349 mg).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 8.13 (s, 1H), 7.40–7.37 (m, 1H), 7.17–7.12 (m, 2H), 6.96–6.94 (m, 1H), 4.69–4.67 (m, 1H), 4.67–4.41 (m, 2H), 3.90 (s, 3H), 3.76–3.74 (m, 1H), 3.73 (s, 3H), 3.27–3.24 (m, 1H), 3.05–3.01 (m, 2H), 2.89–2.84 (m, 1H), 1.53–1.51 (m, 4H), 1.44 (s, 9H).

MS (ESI+) 530 ( $\text{M}^+ + 1$ , 100%).

#### Reference Example 18

tert-Butyl 4-(3-benzyl-5-methyl-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-2-yl)piperazin-1-carboxylate



(Methylamino)acetaldehyde dimethyl acetal (69.5 mg) was added to a solution of 4-benzyl-3-[4-(tert-butoxycarbonyl)piperazin-1-yl]-1H-pyrazole-5-carboxylic acid (150 mg), 1-hydroxy-1H-benzotriazole (52.5 mg) and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (74.5 mg) in N,N-dimethylformamide (1.5 ml), and the resulting mixture was stirred at room temperature for 24 hours. The reaction solution was poured into water (50 ml) and extracted with toluene/ethyl acetate (1 : 1, 100 ml). The extracted solution was dried over

anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The oil thus obtained was dissolved in 1,4-dioxane (15 ml), followed by adding thereto 1N hydrochloric acid (3 ml), and the resulting mixture was stirred at 50°C for 2 hours. The reaction solution was cooled to room temperature and made basic with a saturated aqueous sodium hydrogencarbonate solution. Di-tert-butyl dicarbonate (170 mg) was added to the thus treated reaction solution and the resulting mixture was stirred at room temperature for 2 hours. The reaction solution was extracted twice with ethyl acetate (100 ml). The combined organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 1/1) to obtain the title compound (102 mg) as a white solid.

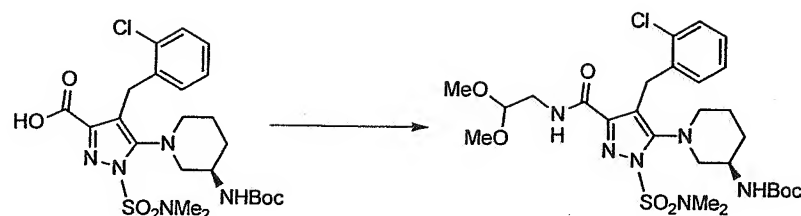
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.25-7.21 (m, 5H), 7.17-7.14 (m, 1H), 6.42 (d, J = 5.9 Hz, 1H), 4.34 (s, 2H), 3.46 (s, 3H), 3.42 (t, J = 5.1 Hz, 4H), 3.04 (t, J = 5.1 Hz, 4H), 1.45 (s, 9H).

MS (ESI+) 424 (M<sup>+</sup>+1, 100%).

## Reference Example 19

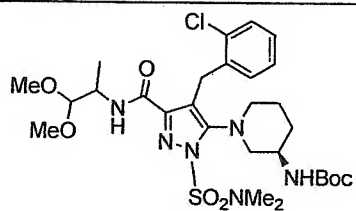
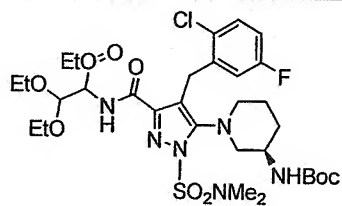
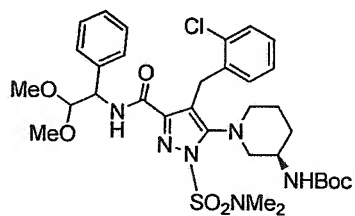
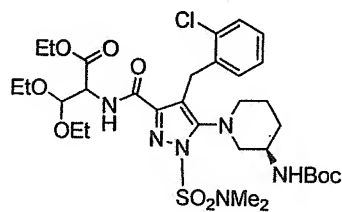
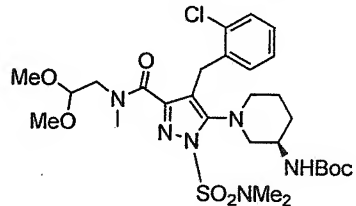
tert-Butyl ((3R)-1-{4-(2-chlorobenzyl)-3-  
 {[(2,2-dimethoxyethyl)amino]carbonyl}-1-  
 [(dimethylamino)sulfonyl]-1H-pyrazol-5-yl}piperidin-3-

yl) carbamate



Aminoacetaldehyde dimethyl acetal (1.20 ml),  
 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide  
 hydrochloride (2.12 g), 1-hydroxybenzotriazole  
 5 monohydrate (1.50 g) and triethylamine (1.54 ml) were  
 added to a solution of 5-((3R)-3-((tert-  
 butoxycarbonyl)amino)piperidin-1-yl)-4-(2-  
 chlorobenzyl)-1-((dimethylamino)sulfonyl)-1H-pyrazole-  
 3-carboxylic acid (3.00 g) in N,N-dimethylformamide  
 10 (6.0 ml), and the resulting mixture was stirred  
 overnight at room temperature. A saturated aqueous  
 sodium hydrogencarbonate solution (200 ml) was added  
 thereto, followed by two runs of extraction with ethyl  
 acetate (100 ml), and the combined organic layer was  
 15 concentrated under reduced pressure to obtain the title  
 compound as a crude product (2.97).  
 MS (ESI+) 629 ( $M^+ + 1$ , 75%).

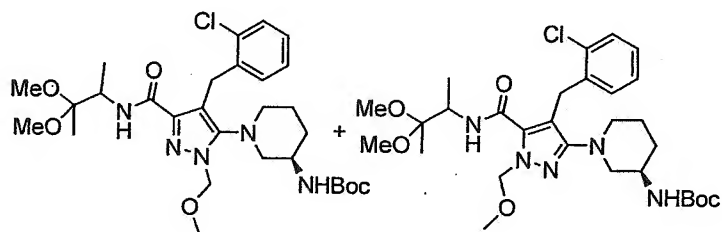
Compounds of Reference Examples 19-1 to 19-8  
 were synthesized by the same process as above.

Reference  
example numberReference  
example numberReference  
Example 19-1Reference  
Example 19-4Reference  
Example 19-2Reference  
Example 19-5Reference  
Example 19-3

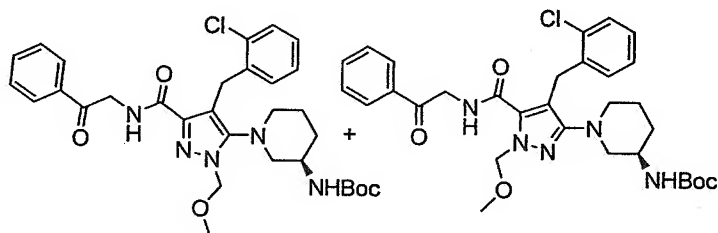
Reference  
example number

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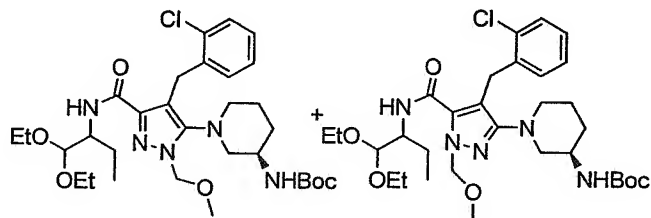
Reference  
Example 19-6



Reference  
Example 19-7

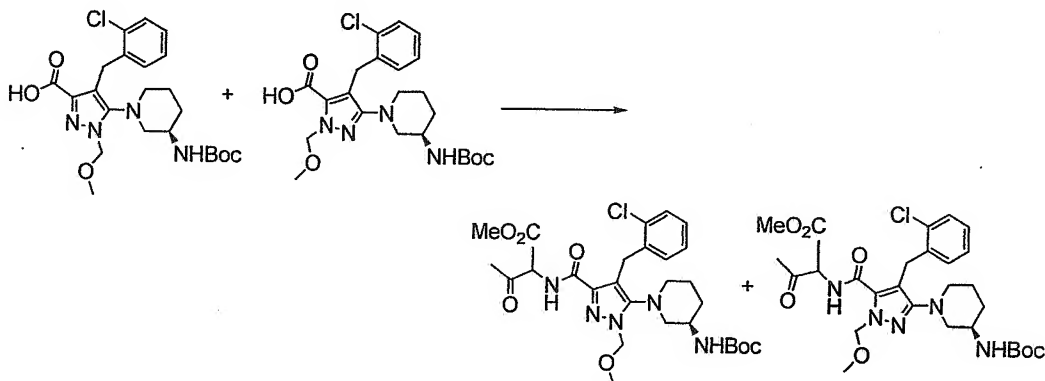


Reference  
Example 19-8



## Reference Example 20

Methyl 2-({[5-((3R)-3-[(tert-butoxycarbonyl)-amino]piperidin-1-yl)-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazol-3-yl]carbonyl}amino)-3-oxobutanoate mixture

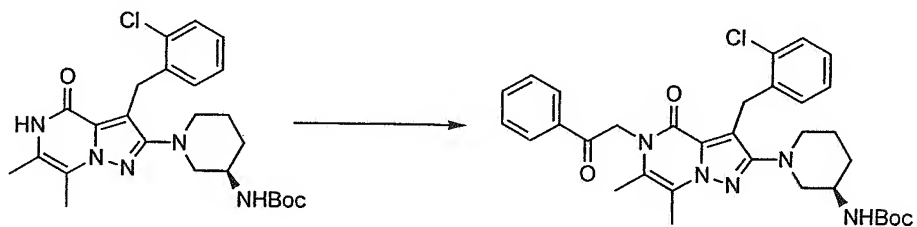


N-methylmorpholine (46.5 mg) and isobutyl chlorocarbonate (62.7 mg) were added to a solution of a 5-((3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl)-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazole-3-carboxylic acid mixture (200.0 mg) in tetrahydrofuran (5 ml), and the resulting mixture was stirred at -20°C for 30 minutes. Then, methyl 2-amino-3-oxobutanoate hydrochloride (200.0 mg) was added thereto, followed by adding dropwise thereto N-methylmorpholine (120.7 mg) slowly, and the resulting mixture was stirred overnight while being slowly warmed from -20°C to room temperature. A 10% aqueous potassium hydrogensulfate solution (50 ml) was added to the reaction solution and organic substances were extracted twice therefrom with ethyl acetate (30 ml). The combined organic layer was washed with a saturated aqueous sodium chloride

solution (50 ml), dried over anhydrous magnesium sulfate and then filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel thin-layer chromatography (hexane/ethyl acetate = 2/1) to obtain the title compound (91.5 mg).  
 MS (ESI+) 593 ( $M^+ + 1$ , 100%).

## Reference Example 21

tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-6,7-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-pyrazolo[1,5-a]pyrazin-2-yl]piperidin-3-yl}carbamate

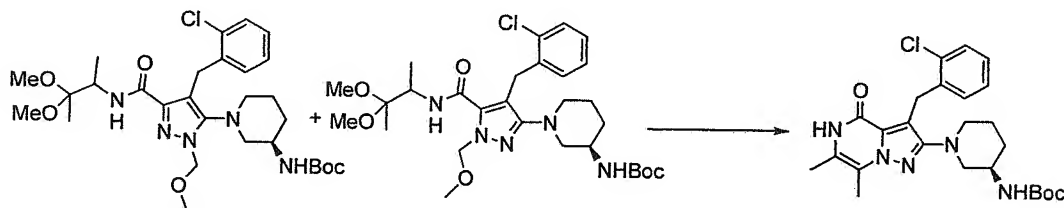


Phenacyl bromide (57.7 mg) and potassium carbonate (79.9 mg) were added to a solution of tert-butyl {(3R)-1-[3-(2-chlorobenzyl)-6,7-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-pyrazolo[1,5-a]pyrazin-2-yl]piperidin-3-yl}carbamate (94.0 mg) in N,N-dimethylformamide (2.0 ml), and the resulting mixture was stirred overnight at room temperature. Water (20 ml) was added to the reaction mixture, followed by two runs of extraction with ethyl acetate (20 ml), and the combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a preparative thin-

layer silica gel chromatography (chloroform/ethyl acetate = 20/1) to obtain the title compound (40.0 mg). MS (ESI+) 604 ( $M^+ + 1$ , 86%).

## Reference Example 22

- 5                   tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-6,7-dimethyl-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-2-yl]piperidin-3-yl}carbamate



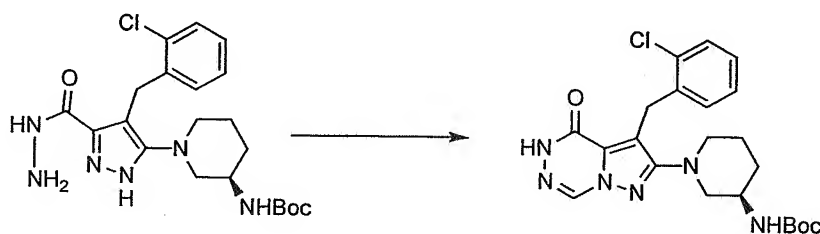
- Water (2.0 ml) and a 4N hydrochloric acid/1,4-dioxane solution (4.0 ml) were added to a solution of a tert-butyl {(3R)-1-[4-(2-chlorobenzyl)-3-  
10 {[(2,2-dimethoxy-1-methylpropyl)amino]carbonyl}-1-(methoxymethyl)-1H-pyrazol-5-yl]piperidin-3-yl}carbamate mixture (430 mg) in 1,4-dioxane (2.0 ml), and the resulting mixture was stirred at 50°C for 2  
15 hours. The reaction mixture was cooled to 0°C and 1,4-dioxane (3.0 ml), water (1.0 ml) and sodium hydrogencarbonate (3.0 g) were added thereto. The resulting mixture was warmed to room temperature and di-tert-butyl dicarbonate (182 mg) was added thereto  
20 and stirred overnight. The 1,4-dioxane was distilled off under reduced pressure and water (50 ml) was added to the residue, followed by two runs of extraction with

ethyl acetate (50 ml). The combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (chloroform/ethyl acetate = 1/1) to obtain the title compound (96.4 mg).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 9.40 (s, 1H), 7.38-7.34 (m, 1H), 7.14-7.02 (m, 2H), 7.01-6.99 (m, 1H), 5.11-5.09 (m, 1H), 4.57-4.36 (m, 2H), 3.78-3.76 (m, 1H), 3.18-3.02 (m, 3H), 2.80-2.78 (m, 1H), 2.39 (s, 3H), 2.14 (s, 3H), 1.54-1.48 (m, 4H), 1.44 (s, 9H). MS (ESI+) 486 (M<sup>+</sup>+1, 56%).

#### Reference Example 23

tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-4-oxo-4,5-dihydropyrazolo[1,5-d][1,2,4]triazin-2-yl]piperidin-3-yl}carbamate



Trimethyl orthoformate (1.09 ml) was added to a solution of tert-butyl {(3R)-1-[4-(2-chlorobenzyl)-3-(hydrazinecarbonyl)-1H-pyrazol-5-yl]piperidin-3-yl}carbamate (478 mg) in a mixture of N,N-dimethylformamide (8 ml) and acetic acid (2 ml), and the resulting mixture was stirred with heating at 80°C for 3 hours. The reaction solution was cooled to room

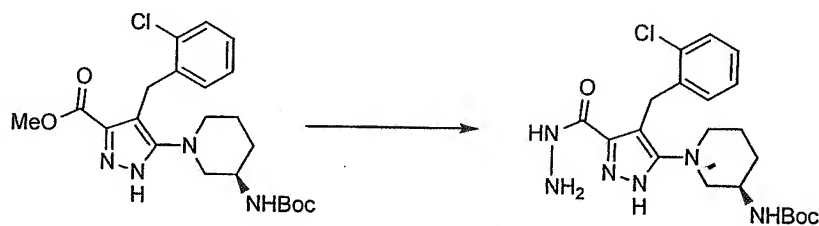
temperature and toluene (20 ml) was added thereto and then distilled off under reduced pressure. This procedure was repeated four times. A 10% aqueous potassium carbonate solution (50 ml) was added to the residue, followed by two runs of extraction with chloroform (50 ml). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 4/1 to 2/1) to obtain the title compound (274 mg) as a white solid.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 9.93 (s, 1H), 8.19 (s, 1H), 7.41-7.36 (m, 1H), 7.19-7.14 (m, 2H), 6.99-6.96 (m, 1H), 4.64-4.62 (m, 1H), 4.54-4.39 (m, 2H), 3.70 (bs, 1H), 3.32-3.29 (m, 1H), 3.06-2.92 (m, 3H), 1.76-1.65 (m, 2H), 1.51-1.45 (m, 2H), 1.44 (s, 9H).

MS (ESI+) 459 ( $\text{M}^+ + 1$ , 52%).

## Reference Example 24

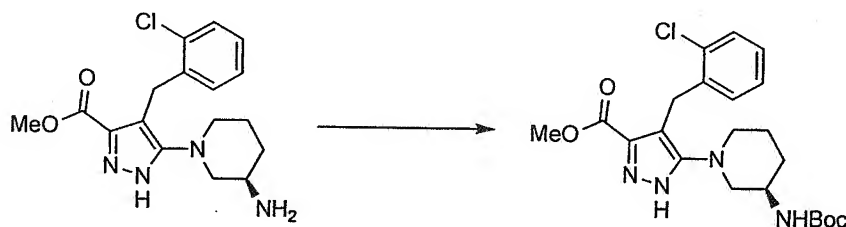
tert-Butyl {(3R)-1-[4-(2-chlorobenzyl)-3-(hydrazinecarbonyl)-1H-pyrazol-5-yl]piperidin-3-yl}carbamate



Hydrazine monohydrate (2.0 ml) was added to methyl 5-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-4-(2-chlorobenzyl)-1H-pyrazole-3-carboxylate (449 mg), and the resulting mixture was stirred with heating at 110°C for 15 hours. The reaction solution was cooled to room temperature and a 10% aqueous potassium carbonate solution (40 ml) was added thereto, followed by extraction with ethyl acetate (100 ml). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain the title compound (274 mg). MS (ESI+) 449 ( $M^+ + 1$ , 100%).

## Reference Example 25

Methyl 5-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-4-(2-chlorobenzyl)-1H-pyrazole-3-carboxylate



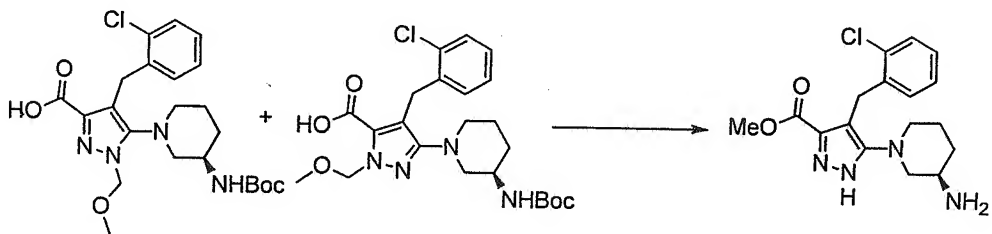
A saturated aqueous sodium hydrogencarbonate solution (10 ml) and di-tert-butyl dicarbonate (218 mg) were added to a solution of methyl 5-[(3R)-3-aminopiperidin-1-yl]-4-(2-chlorobenzyl)-1H-pyrazole-3-carboxylate (180 mg) in tetrahydrofuran (10 ml), and the resulting mixture was vigorously stirred overnight

at room temperature. Tetrahydrofuran was distilled off under reduced pressure and the residue was extracted twice with chloroform (50 ml). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 3/1 to 1/1) to obtain the title compound (191 mg) as a white solid.

- <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 7.39-7.36 (m, 1H), 7.16-7.11 (m, 2H), 6.94-6.91 (m, 1H), 4.92-4.90 (m, 1H), 4.29-4.11 (m, 2H), 3.86-3.77 (m, 1H), 3.82 (s, 3H), 3.18-3.14 (m, 1H), 2.90-2.80 (m, 3H), 1.64-1.46 (m, 4H), 1.44 (s, 9H).
- MS (ESI+) 449 (M<sup>+</sup>+1, 85%).

#### Reference Example 26

Methyl 5-[(3R)-3-aminopiperidin-1-yl]-4-(2-chlorobenzyl)-1H-pyrazole-3-carboxylate



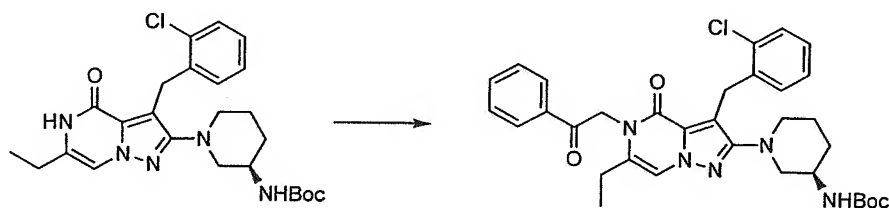
- A solution of a 5-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazole-3-carboxylic acid mixture (240 mg) in 10% hydrochloric

acid/methanol (10 ml) was stirred in a sealed tube with heating at 80°C for 8 hours. The reaction solution was cooled to room temperature and then distilled under reduced pressure to remove the solvent, whereby the  
 5 title compound was obtained as a crude product (180 mg).

MS (ESI+) 349 ( $M^+ + 1$ , 60%).

#### Reference Example 27

tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-6-ethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydropyrazolo[1,5-a]pyrazin-2-yl]piperidin-3-yl}carbamate  
 10



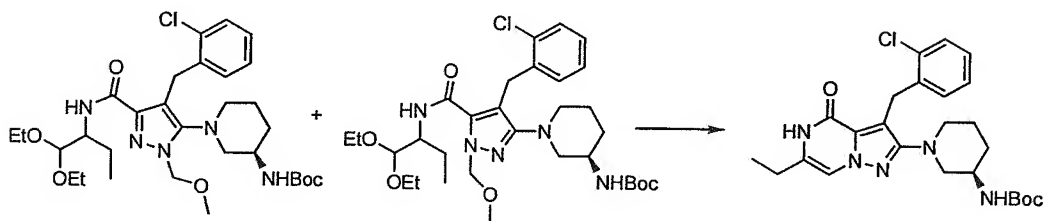
Phenacyl bromide (36.9 mg) and potassium carbonate (50.9 mg) were added to a solution of tert-butyl {(3R)-1-[3-(2-chlorobenzyl)-6-ethyl-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-2-yl]piperidin-3-yl}carbamate (60.0 mg) in N,N-dimethylformamide (1.5 ml), and the resulting mixture was stirred overnight at room temperature. Water (20 ml) was added to the  
 15 reaction mixture, followed by two runs of extraction with ethyl acetate (20 ml), and the combined organic layer was concentrated under reduced pressure. The  
 20

resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 2/1) to obtain the title compound (23.2 mg).

MS (ESI+) 604 ( $M^+ + 1$ , 100%).

## 5 Reference Example 28

tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-6-ethyl-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-2-yl]piperidin-3-yl}carbamate



- Water (2.5 ml) and a 4N hydrochloric acid/1,4-dioxane solution (5.0 ml) were added to a solution of a tert-butyl {(3R)-1-[4-(2-chlorobenzyl)-3-([1-(dimethoxymethyl)propyl]amino)carbonyl]-1-(methoxymethyl)-1H-pyrazol-5-yl]piperidin-3-yl}carbamate mixture (324 mg) in 1,4-dioxane (2.5 ml), and the resulting mixture was stirred at 50°C for 2 hours. The reaction mixture was cooled to 0°C and 1,4-dioxane (4.0 ml), water (2.0 ml) and sodium hydrogen-carbonate (3.8 g) were added thereto. The resulting mixture was warmed to room temperature and di-tert-butyl dicarbonate (228 mg) was added thereto and stirred overnight. 1,4-dioxane was distilled off under reduced pressure and water (50 ml) was added to the

residue, followed by two runs of extraction with ethyl acetate (50 ml). The combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a silica gel column

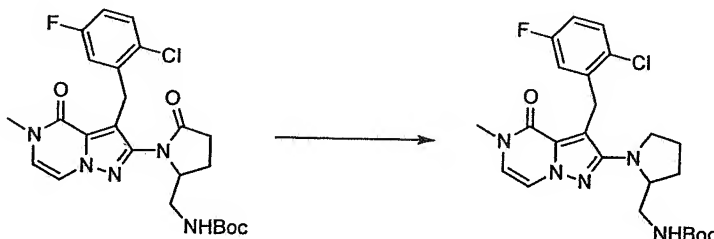
5 chromatography (hexane/ethyl acetate = 2/1) to obtain the title compound (80.9 mg).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 9.47 (s, 1H), 7.39-7.36 (m, 1H), 7.14-7.11 (m, 2H), 7.06-7.05 (m, 1H), 7.02-7.00 (m, 1H), 4.83-4.80 (m, 1H), 4.54-4.34 (m, 2H),  
10 3.85-3.82 (m, 1H), 3.16-3.15 (m, 1H), 3.01-2.98 (m, 2H), 2.85-2.81 (m, 1H), 2.45-2.39 (m, 2H), 1.57-1.49 (m, 4H), 1.44 (s, 9H), 1.21 (t, J = 7.5 Hz, 3H).

MS (ESI+) 486 (M<sup>+</sup>+1, 67%).

#### Reference Example 29

15 tert-Butyl ({1-[3-(2-chloro-5-fluorobenzyl)-5-methyl-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-2-yl]pyrrolidin-2-yl)methyl} carbamate

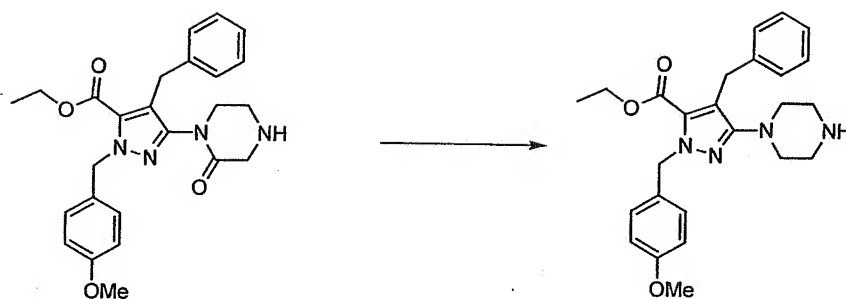


A reactor containing a solution of tert-butyl  
({1-[3-(2-chloro-5-fluorobenzyl)-5-methyl-4-oxo-4,5-  
20 dihydropyrazolo[1,5-a]pyrazin-2-yl]-5-oxopyrrolidin-2-yl)methyl} carbamate (406.1 mg) in tetrahydrofuran (50 ml) was cooled with a water-ice bath. To this solution

was added a borane-tetrahydrofuran complex (a 1.1M tetrahydrofuran solution, 7.33 ml), and the resulting mixture was stirred at room temperature for 2 hours. The reactor was cooled again with a water-ice bath and 5 methanol (10 ml) was added. Then, the resulting mixture was stirred at room temperature for 30 minutes and the reaction solution was concentrated under reduced pressure. The resulting oil was dissolved in methanol (30 ml) and the resulting solution was 10 concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 5/1 to 1/1) to obtain the title compound (69.1 mg) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.34-7.30 (m, 1H), 7.23 15 (d, J = 6.0 Hz, 1H), 6.85-6.80 (m, 1H), 6.63-6.60 (m, 1H), 6.42 (d, J = 6.0 Hz, 1H), 4.79 (br, 1H), 4.60 (d, J = 17.9 Hz, 1H), 4.39 (d, J = 17.9 Hz, 1H), 4.08-4.02 (m, 1H), 3.45 (s, 3H), 3.46-3.40 (m, 1H), 3.32-3.26 (m, 2H), 3.08-3.02 (m, 1H), 1.94-1.71 (m, 4H), 1.42 (s, 20 9H). MS (ESI+) 490 (M<sup>+</sup>+1, 100%).

#### Reference Example 30

Ethyl 4-benzyl-1-(4-methoxybenzyl)-3-piperazin-1-yl-1H-pyrazole-5-carboxylate



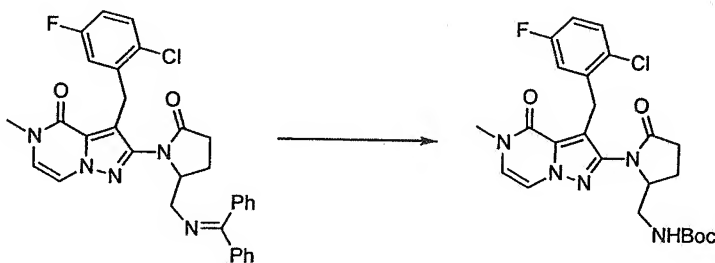
The title compound (1.22 g) was synthesized by the same process as in Reference Example 29.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.25-7.06 (m, 7H), 6.85-6.80 (m, 2H), 5.59 (s, 2H), 4.11 (q,  $J = 7.1$  Hz, 2H),  
 5 4.03 (s, 2H), 3.77 (s, 3H), 3.08-2.94 (m, 4H), 2.75-2.71 (m, 2H), 2.56-2.50 (m, 2H), 1.02 (t,  $J = 7.1$  Hz, 3H).

MS (ESI+) 435 ( $M^+ + 1$ , 100%).

#### Reference Example 31

10 tert-Butyl ({1-[3-(2-chloro-5-fluorobenzyl)-5-methyl-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-2-yl]-5-oxopyrrolidin-2-yl}methyl)carbamate



To a solution of 3-(2-chloro-5-fluorobenzyl)-  
 2-(2-{{(diphenylmethylene)amino}methyl})-5-  
 15 oxopyrrolidin-1-yl)-5-methylpyrazolo[1,5-a]pyrazin-

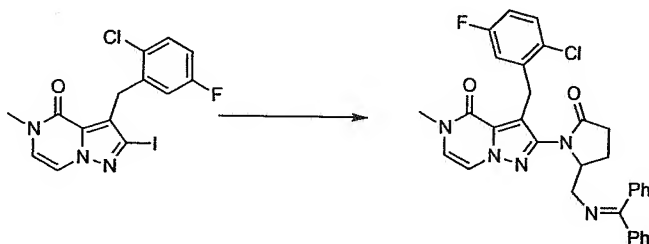
4(5H)-one (663.6 mg) in tetrahydrofuran (20 ml) was added 1N hydrochloric acid (10 ml), and the resulting mixture was stirred at room temperature for 1 hour. Tetrahydrofuran was removed under reduced pressure and the residue was extracted twice with diethyl ether (20 ml). After the aqueous layer was concentrated under reduced pressure, toluene was added thereto and the resulting mixture was similarly concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (50 ml), followed by adding thereto a saturated aqueous sodium hydrogencarbonate solution (10 ml) and then di-tert-butyl dicarbonate (511 mg), and the resulting mixture was stirred at room temperature for 2 hours. The reaction solution was extracted twice with ethyl acetate (20 ml). The combined organic layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 1/1) to obtain the title compound (408.9 mg) as a white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.33 (d,  $J = 6.0$  Hz, 1H), 7.30-7.28 (m, 1H), 6.98-6.94 (m, 1H), 6.89-6.84 (m, 1H), 6.62 (d,  $J = 6.0$  Hz, 1H), 4.89 (br, 1H), 4.59 (d,  $J = 16.1$  Hz, 1H), 4.37 (d,  $J = 16.1$  Hz, 1H), 3.62-3.58 (m, 1H), 3.53 (s, 3H), 3.37-3.31 (m, 1H), 3.00-2.94 (m, 1H), 2.52-2.32 (m, 2H), 2.09-1.90 (m, 2H), 1.42 (s, 9H).

MS (ESI+) 504 ( $M^+ + 1$ , 100%).

Reference Example 32

3-(2-Chloro-5-fluorobenzyl)-2-(2-((diphenylmethylene)amino)methyl)-5-oxopyrrolidin-1-yl)-5-methylpyrazolo[1,5-a]pyrazin-4(5H)-one



A mixture of 3-(2-chloro-5-fluorobenzyl)-2-iodo-5-methylpyrazolo[1,5-a]pyrazin-4(5H)-one (908 mg), 5-((diphenylmethylene)amino)methylpyrrolidin-2-one (1.21 g), potassium phosphate (924 mg), copper(I) iodide (87 mg), 1,4-dioxane (10 ml) and N,N'-dimethylethylenediamine (767 mg) was stirred at 100°C for 50 hours. The reaction mixture was cooled to room temperature and then filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (chloroform/methanol = 95.5/0.5) to obtain the title compound (663.6 mg) as a yellow solid.

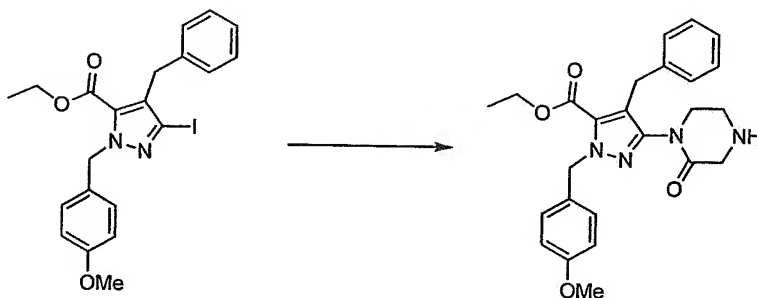
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.52-7.25 (m, 8H), 7.23 (d,  $J$  = 6.0 Hz, 1H), 7.08-7.05 (m, 1H), 7.04-7.00 (m, 2H), 6.84-6.81 (m, 1H), 6.71-6.66 (m, 1H), 6.54 (d,  $J$  = 6.0 Hz, 1H), 4.46 (d,  $J$  = 16.4 Hz, 1H), 4.38 (d,  $J$  = 16.4 Hz, 1H), 4.28-4.23 (m, 1H), 3.48 (s, 3H), 3.38

(dd,  $J = 14.4$  and  $3.8$  Hz, 1H), 3.21 (dd,  $J = 14.4$  and  $6.2$  Hz, 1H), 2.64-2.56 (m, 1H), 2.45-2.37 (m, 1H), 2.27-2.17 (m, 1H), 1.94-1.85 (m, 1H).

MS (ESI+) 568 ( $M^+ + 1$ , 100%).

#### 5 Reference Example 33

Ethyl 4-benzyl-1-(4-methoxybenzyl)-3-(2-oxopiperazin-1-yl)-1H-pyrazole-5-carboxylate



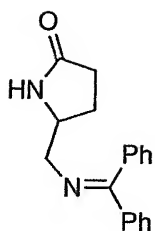
The title compound (2.21 g) was synthesized by the same process as in Reference Example 32.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 7.29-7.18 (m, 5H), 7.14-7.12 (m, 2H), 6.84 (d,  $J = 8.7$  Hz, 2H), 5.63 (s, 2H), 4.31 (q,  $J = 7.1$  Hz, 2H), 4.09 (s, 2H), 3.78 (s, 3H), 3.41 (s, 2H), 3.21 (t,  $J = 5.5$  Hz, 2H), 2.74 (t,  $J = 5.5$  Hz, 2H), 1.28 (t,  $J = 7.1$  Hz, 3H).

MS (ESI+) 449 ( $M^+ + 1$ , 100%).

#### Reference Example 34

5-[(Diphenylmethylene)amino]methyl}-pyrrolidin-2-one



In methanol (500 ml) was suspended 4,5-diaminovaleric acid dihydrochloride (9.40 g), and the resulting suspension was stirred at room temperature for 3 hours. To the resulting transparent solution was added sodium carbonate (11.56 g), and the resulting mixture was stirred at room temperature for 2 days. The reaction mixture was filtered and benzophenoneimine (16.62 g) was added to the filtrate, followed by stirring at room temperature for 24 hours. The reaction solution was concentrated and the residue was suspended in ethyl acetate. The resulting suspension was filtered and the filtrate was concentrated. The resulting residue was purified by a silica gel column chromatography (ethyl acetate) to obtain the title compound (1.21 g) as an oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  ppm 7.63–7.33 (m, 8H), 7.20–7.17 (m, 2H), 4.02–3.98 (m, 1H), 3.44 (d,  $J = 5.5$  Hz, 2H), 2.39–2.27 (m, 3H), 1.94–1.87 (m, 1H).

MS (ESI+) 279 ( $\text{M}^+ + 1$ , 100%).

## 20 Reference Example 35

4-Benzyl-3-[4-(tert-butoxycarbonyl)piperazin-1-yl]-1H-pyrazole-5-carboxylic acid



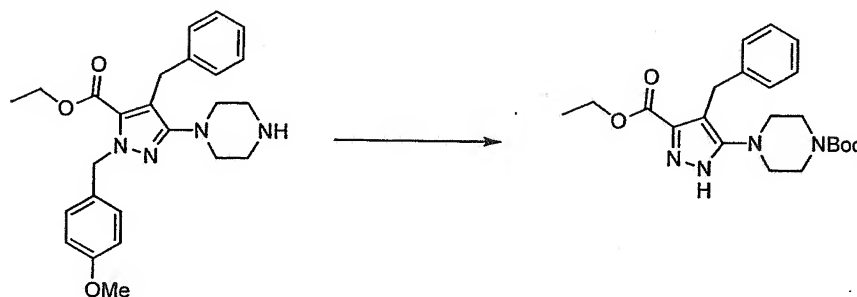
In a mixture of methanol (10 ml) and tetrahydrofuran (10 ml) was dissolved tert-butyl 4-[4-benzyl-3-(ethoxycarbonyl)-1H-pyrazol-5-yl]piperazin-1-carboxylate (732.4 mg), followed by adding thereto a 2N aqueous sodium hydroxide solution (4.4 ml), and the resulting mixture was allowed to stand at room temperature for 24 hours and then stirred at 50°C for 3 hours. The reaction solution was cooled and the tetrahydrofuran was removed under reduced pressure. To the resulting residue was added water (50 ml), and a reactor containing thus obtained mixture was cooled in a water-ice bath. This mixture was acidified with a 5% aqueous potassium hydrogensulfate solution. The reaction solution was extracted twice with ethyl acetate (100 ml). The combined organic layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain the title compound (635 mg) as a white solid.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 7.24-7.11 (m, 5H), 4.12 (s, 2H), 3.39 (t, J = 5.1 Hz, 4H), 2.85 (t, J = 5.1 Hz, 4H), 1.45 (s, 9H).

MS (ESI+) 387 (M<sup>+</sup>+1, 100%).

## Reference Example 36

tert-Butyl 4-[4-benzyl-3-(ethoxycarbonyl)-1H-pyrazol-5-yl]piperazin-1-carboxylate



Ethyl 4-benzyl-1-(4-methoxybenzyl)-3-piperazin-1-yl-1H-pyrazole-5-carboxylate (1.22 g) was dissolved in a mixture of anisole (1.0 ml) and trifluoroacetic acid (16 ml), followed by adding thereto 96% sulfuric acid (0.5 ml), and the resulting mixture was allowed to stand at room temperature for 5 days. The reaction solution was concentrated and tetrahydrofuran (40 ml) was added thereto. A reactor containing the reaction solution was cooled in a water-ice bath and the reaction solution was made basic with a saturated aqueous sodium hydrogencarbonate solution, followed by adding thereto di-tert-butyl dicarbonate (1.23 g). The reaction solution was stirred at room temperature for 2 hours and extracted twice with ethyl acetate (50 ml). The combined organic layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 4/1 to 1/1) to

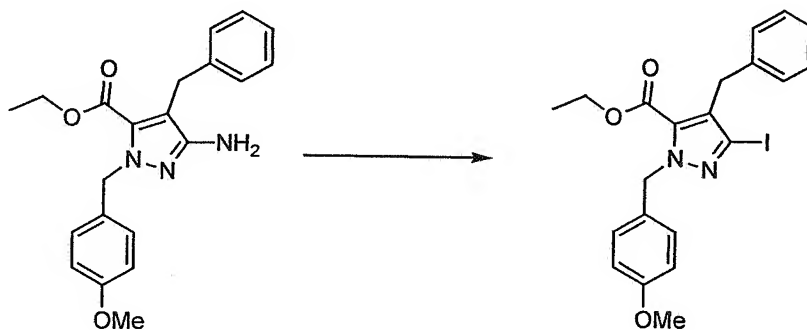
obtain the title compound (732.4 mg) as a white solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.25-7.23 (m, 2H), 7.18-7.15 (m, 3H), 4.30 (q, J = 7.1 Hz, 2H), 4.10 (s, 2H), 3.43 (t, J = 5.1 Hz, 4H), 2.94 (t, J = 5.1 Hz, 4H),  
 5 1.45 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H).

MS (ESI+) 415 (M<sup>+</sup>+1, 100%).

#### Reference Example 37

Ethyl 4-benzyl-3-iodo-1-(4-methoxybenzyl)-1H-pyrazole-5-carboxylate



10 Ethyl 3-amino-4-benzyl-1-(4-methoxybenzyl)-1H-pyrazole-5-carboxylate (14.05 g) was dissolved in a mixture of diiodomethane (32 ml) and isoamyl nitrite (22.6 g), and the resulting solution was stirred at room temperature for 2 hours. The reaction solution  
 15 was concentrated and the resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 12.5/1) to obtain the title compound (9.33 g) as an oil.

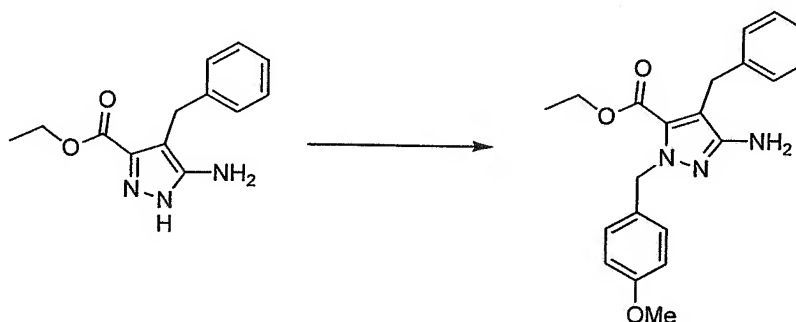
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.26-7.20 (m, 4H), 7.18-7.10 (m, 3H), 6.83 (d, J = 8.7 Hz, 2H), 5.67 (s, 2H),  
 20

4.22 (q,  $J = 7.1$  Hz, 2H), 4.02 (s, 2H), 3.77 (s, 3H),  
1.18 (t,  $J = 7.1$  Hz, 3H).

MS (ESI+) 477 ( $M^+ + 1$ , 100%).

# Reference Example 38

5 Ethyl 3-amino-4-benzyl-1-(4-methoxybenzyl)-  
1H-pyrazole-5-carboxylate



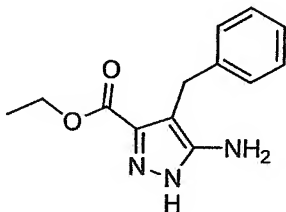
Cesium carbonate (25.0 g) and 4-methoxybenzyl  
chloride (12.02 g) were added to a solution of ethyl 5-  
amino-4-benzyl-1H-pyrazole-3-carboxylate (17.09 g) in  
10 N,N-dimethylformamide (500 ml), and the resulting  
mixture was stirred at 70°C for 15 hours. The reaction  
mixture was cooled to room temperature and filtered,  
and the filtrate was concentrated under reduced  
pressure. The resulting residue was purified by a  
15 silica gel column chromatography (hexane/ethyl acetate  
= 5/1) to obtain the title compound (14.05 g) as an  
oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.29-7.25 (m, 2H), 7.20-  
7.16 (m, 5H), 6.83 (d,  $J = 8.7$  Hz, 2H), 5.51 (s, 2H),  
20 4.27 (q,  $J = 7.1$  Hz, 2H), 4.01 (s, 2H), 3.77 (s, 3H),  
3.43 (br, 2H), 1.24 (t,  $J = 7.1$  Hz, 3H).

MS (ESI+) 366 ( $M^+ + 1$ , 100%).

Reference Example 39

Ethyl 5-amino-4-benzyl-1H-pyrazole-3-carboxylate



- 5                Sodium ethoxide (a 21% ethanol solution, 150 ml) was added to a solution of 3-phenylpropionitrile (43.56 g) and diethyl oxalate (48.53 g) in ethanol (500 ml), and the resulting mixture was stirred with heating under reflux for 10 hours. The reaction solution was
- 10 cooled to room temperature, followed by adding thereto 35% hydrochloric acid (45 g) and then acetic acid (200 ml) and hydrazine monohydrate (21.6 g). The reaction solution was stirred with heating under reflux for 10 hours, cooled to room temperature, and then
- 15 concentrated under reduced pressure. The resulting residue was suspended in ethyl acetate (300 ml) and the resulting suspension was made basic with a saturated aqueous sodium hydrogencarbonate solution and extracted four times with ethyl acetate (500 ml). The combined
- 20 organic layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was

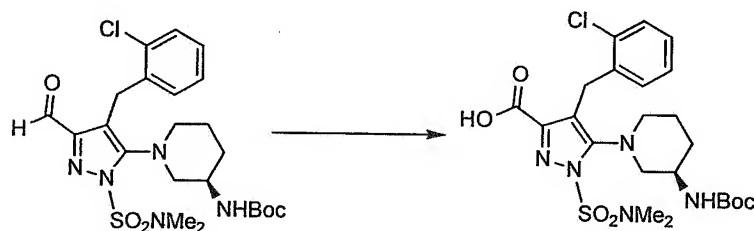
washed 5 times with hexane (500 ml) and dried to obtain the title compound (31.76 g) as a brown solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.30–7.26 (m, 2H), 7.22–7.18 (m, 3H), 4.36 (q,  $J = 7.1$  Hz, 2H), 4.06 (s, 2H),  
 5 3.55 (br, 2H), 1.34 (t,  $J = 7.1$  Hz, 3H).

MS (ESI+) 246 ( $M^+ + 1$ , 100%).

#### Reference Example 40

5-((3R)-3-[(tert-Butoxycarbonyl)amino]-piperidin-1-yl)-4-(2-chlorobenzyl)-1-  
 10 [(dimethylamino)sulfonyl]-1H-pyrazole-3-carboxylic acid



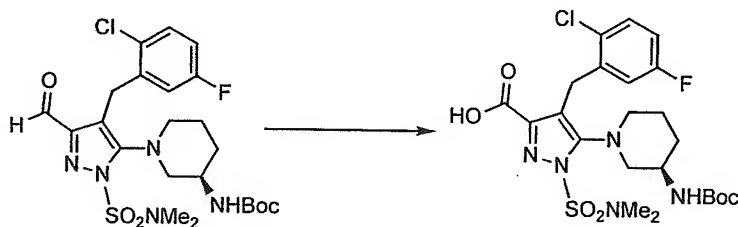
An aqueous solution (80 ml) of sodium dihydrogenphosphate dihydrate (7.69 g) was added to a solution of tert-butyl ((3R)-1-{4-(2-chlorobenzyl)-1-[(dimethylamino)sulfonyl]-3-formyl-1H-pyrazol-5-  
 15 yl}piperidin-3-yl)carbamate (8.64 g) in tert-butyl alcohol (400 ml), and the reaction mixture was ice-cooled. After 2-methyl-2-butene (8.7 ml) and sodium chlorite (1.78 g) were added thereto, the resulting mixture was stirred at 0°C for 3 hours. An aqueous  
 20 solution (50 ml) of sodium sulfite (0.41 g) and a 5% potassium hydrogensulfate solution (1000 ml) were added to the reaction mixture, followed by two runs of

extraction with ethyl acetate (500 ml), and the combined organic layer was concentrated under reduced pressure to obtain the title compound as a crude product (8.88 g).

- 5  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.38-7.36 (m, 1H), 7.12-7.11 (m, 2H), 6.99-6.97 (m, 1H), 4.71-4.68 (m, 1H), 4.09-4.03 (m, 2H), 3.74-3.72 (m, 1H), 3.20-3.19 (m, 1H), 3.06 (s, 6H), 2.99-2.94 (m, 1H), 2.88-2.82 (m, 2H), 1.52-1.47 (m, 4H), 1.44 (s, 9H).
- 10 MS (ESI+) 542 ( $\text{M}^+ + 1$ , 60%).

#### Reference Example 41

5-[(3R)-3-[(tert-butoxycarbonyl)amino]-piperidin-1-yl]-4-(2-chloro-5-fluorobenzyl)-1-[(dimethylamino)sulfonyl]-1H-pyrazole-3-carboxylic acid

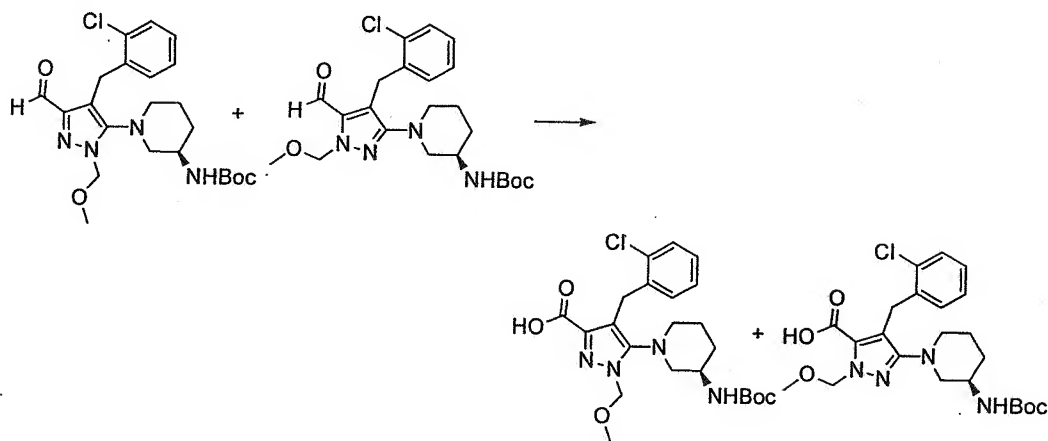


- 15 The title compound was synthesized as a crude product (4.2 g) by the same process as in Reference Example 40.
- MS (ESI+) 560 ( $\text{M}^+ + 1$ , 47%).

#### Reference Example 42

- 20 5-[(3R)-3-[(tert-butoxycarbonyl)amino]-piperidin-1-yl]-4-(2-chlorobenzyl)-1-(methoxymethyl)-

## 1H-pyrazole-3-carboxylic acid mixture



An aqueous solution (12.46 g / 30 ml water) of sodium dihydrogenphosphate dihydrate was added to a solution of a tert-butyl ((3R)-1-[4-(2-chlorobenzyl)-3-formyl-1-(methoxymethyl)-1H-pyrazol-5-yl]piperidin-3-yl)carbamate mixture (12.33 g) in tert-butanol (140 ml), and the resulting mixture was cooled to 0°C. To the reaction solution were added dropwise 2-methyl-2-butene (14.11 ml) and an aqueous sodium chlorite solution (3.66 g / 20 ml water), and the resulting mixture was vigorously stirred at 0°C for 7 hours. After a 1M aqueous sodium sulfite solution (55 ml) was added thereto, the resulting mixture was adjusted to pH2 with a 10% aqueous potassium hydrogensulfate solution (200 ml) and extracted twice with ethyl acetate (300 ml). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain the title compound (12.73 g) as a light-yellow solid.

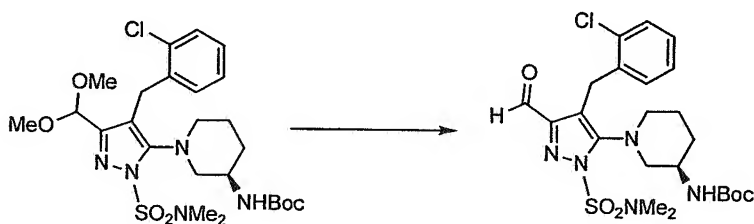
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 7.37-7.34 (m, 1H), 7.12-

7.08 (m, 2H), 6.88-6.81 (m, 1H), 5.73-5.69 (m, 2H),  
4.90-4.88 (m, 1H), 4.25-4.10 (m, 2H), 3.74-3.72 (m,  
1H), 3.39-3.32 (m, 3H), 3.11-3.08 (m, 1H), 2.86-2.71  
(m, 3H), 1.54-1.46 (m, 4H), 1.43-1.41 (m, 9H).

5 MS (ESI+) 479 ( $M^+ + 1$ , 37%).

#### Reference Example 43

tert-Butyl ((3R)-1-{4-(2-chlorobenzyl)-1-  
[(dimethylamino)sulfonyl]-3-formyl-1H-pyrazol-5-  
yl}piperidin-3-yl)carbamate



10 Acetic acid (100 ml) and water (50 ml) were  
added to a solution of tert-butyl ((3R)-1-{4-(2-  
chlorobenzyl)-3-(dimethoxymethyl)-1-  
[(dimethylamino)sulfonyl]-1H-pyrazol-5-yl}piperidin-3-  
yl)carbamate (10.2 g) in 1,4-dioxane (50 ml), and the  
15 resulting mixture was stirred at 50°C for 8 hours. The  
reaction mixture was concentrated under reduced  
pressure and water (500 ml) was added to the residue,  
followed by two runs of extraction with ethyl acetate  
(300 ml). The combined organic layer was concentrated  
20 under reduced pressure to obtain the title compound as  
a crude product (9.49 g).

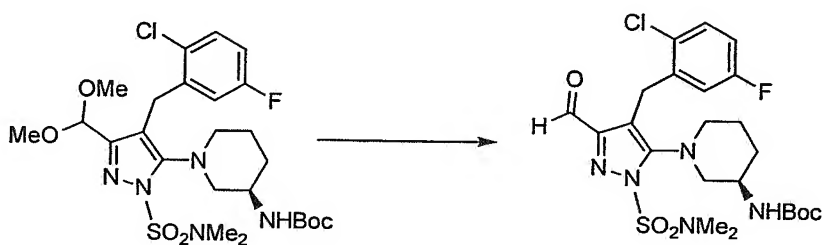
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 10.41 (s, 1H), 7.40-7.37

(m, 1H), 7.19-7.13 (m, 2H), 6.88-6.77 (m, 1H), 4.68-4.66 (m, 1H), 4.31-4.14 (m, 2H), 3.75-3.73 (m, 1H), 3.07 (s, 6H), 2.99-2.94 (m, 2H), 2.92-2.76 (m, 2H), 1.65-1.49 (m, 4H), 1.43 (s, 9H).

5 MS (ESI+) 526 ( $M^+ + 1$ , 50%).

## Reference Example 44

tert-Butyl ((3R)-1-{4-(2-chloro-5-fluorobenzyl)-1-[(dimethylamino)sulfonyl]-3-formyl-1H-pyrazol-5-yl}piperidin-3-yl)carbamate

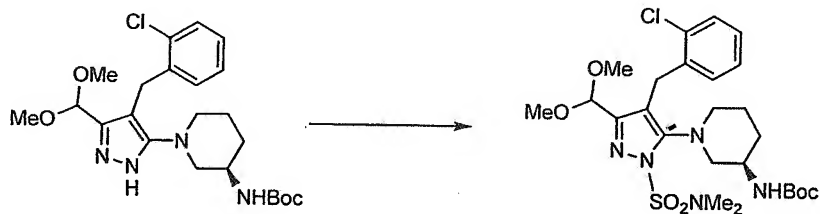


10 The title compound (4.3 g) was synthesized by the same process as in Reference Example 43.

MS (ESI+) 544 ( $M^+ + 1$ , 44%).

## Reference Example 45

tert-Butyl ((3R)-1-{4-(2-chlorobenzyl)-3-(dimethoxymethyl)-1-[(dimethylamino)sulfonyl]-1H-pyrazol-5-yl}piperidin-3-yl)carbamate



Triethylamine (5.5 ml) and potassium tert-butoxide (13.4 g) were added to a solution of tert-butyl ((3R)-1-[4-(2-chlorobenzyl)-3-(dimethoxymethyl)-1H-pyrazol-5-yl]piperidin-3-yl)carbamate (18.6 g) in 5 N,N-dimethylformamide (160 ml) under ice-cooling, and the resulting mixture was warmed to room temperature and then stirred for 1 hour. The reaction mixture was ice-cooled again and N,N-dimethylsulfonyl chloride (6.73 ml) was added thereto and stirred for 2 hours.

10 Water (500 ml) was added to the reaction mixture, followed by two runs of extraction with ethyl acetate (300 ml), and the combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a silica gel column

15 chromatography (hexane/ethyl acetate = 3/1) to obtain the title compound (10.2 g).

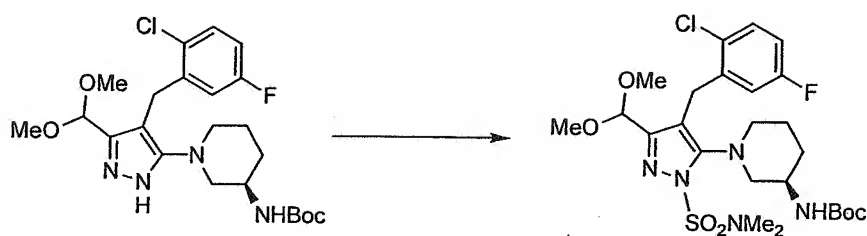
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.38-7.36 (m, 1H), 7.18-7.12 (m, 2H), 6.98-6.96 (m, 1H), 5.89 (s, 1H), 4.67-4.65 (m, 1H), 4.27-4.07 (m, 2H), 3.71-3.70 (m, 1H), 20 3.37 (s, 6H), 3.04 (s, 6H), 3.05-3.01 (m, 3H), 2.69-2.64 (m, 1H), 1.53-1.52 (m, 2H), 1.44 (s, 9H), 1.39-1.37 (m, 2H).

MS (ESI+) 572 (M<sup>+</sup>+1, 31%).

## Reference Example 46

25 tert-Butyl ((3R)-1-{4-(2-chloro-5-fluorobenzyl)-3-(dimethoxymethyl)-1-[(dimethylamino)sulfonyl]-1H-pyrazol-5-yl}piperidin-3-

yl) carbamate



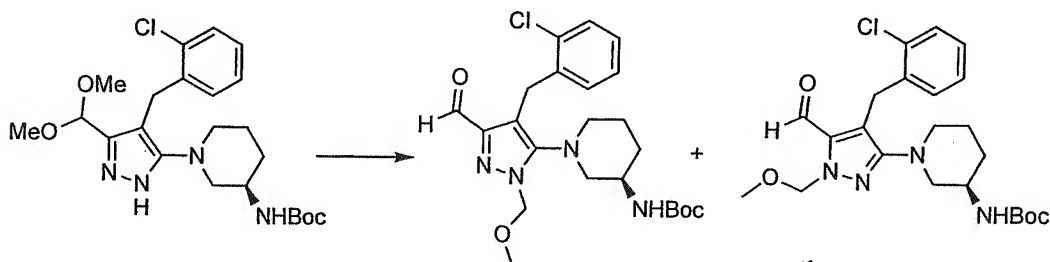
The title compound (4.6 g) was synthesized by the same process as in Reference Example 45.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.37-7.30 (m, 1H), 6.90-6.82 (m, 1H), 6.78-6.69 (m, 1H), 5.89 (s, 1H), 4.14 (d, J = 18Hz, 1H), 4.06 (d, J = 18Hz, 1H), 3.77-3.68 (m, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 3.05 (s, 3H), 2.99-2.86 (m, 2H), 2.82 (s, 3H), 2.80-2.70 (m, 1H), 1.64-1.36 (m, 5H), 1.43 (s, 9H).

MS (ESI+) 590 (M<sup>+</sup>+1, 67%).

#### Reference Example 47

tert-Butyl {(3R)-1-[4-(2-chlorobenzyl)-3-formyl-1-(methoxymethyl)-1H-pyrazol-5-yl]piperidin-3-yl} carbamate mixture



A solution (60 ml) of tert-butyl {(3R)-1-[4-(2-chlorobenzyl)-3-(dimethoxymethyl)-1H-pyrazol-5-

yl]piperidin-3-yl}carbamate (15.00 g) in N,N-dimethylformamide was cooled to 0°C and 55% sodium hydride (1.69 g) was added thereto. The resulting mixture was warmed to room temperature 30 minutes after the addition and then stirred for 30 minutes. The reaction solution was cooled to 0°C again and chloromethyl methyl ether (3.27 g) was added thereto. The resulting mixture was warmed to room temperature 4 hours after the addition and then stirred for 1 day. Water (500 ml) was added to the reaction solution, followed by extraction with ethyl acetate (500 ml). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The crude product thus obtained was made into a mixed solution with 1,4-dioxane (50 ml), water (50 ml) and acetic acid (150 ml), and the mixed solution was stirred with heating at 50°C for 6 hours. The mixed solution was cooled to 0°C, adjusted to pH 9 with an aqueous sodium carbonate solution, and then extracted twice with ethyl acetate (300 ml). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 4/1 to 1/1) to obtain the title compound (8.62 g) as a light-yellow liquid.

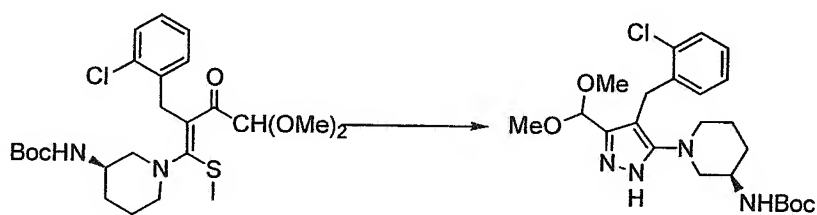
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 9.83 (s, 1H), 7.41-7.35

(m, 1H), 7.20-7.17 (m, 2H), 7.03-7.00 (m, 1H), 5.65 (s, 2H), 4.82-4.80 (m, 1H), 4.26-4.18 (m, 2H), 3.77-3.75 (m, 1H), 3.36 (s, 3H), 3.20-3.17 (m, 1H), 2.93-2.84 (m, 3H), 1.64-1.47 (m, 4H), 1.43 (s, 9H).

5 MS (ESI+) 463 ( $M^+ + 1$ , 70%).

#### Reference Example 48

tert-Butyl {(3R)-1-[4-(2-chlorobenzyl)-3-(dimethoxymethyl)-1H-pyrazol-5-yl]piperidin-3-yl}carbamate



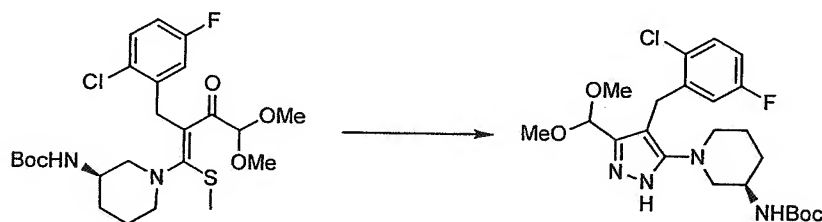
10                   Hydrazine monohydrate (6.91 ml) was added to a solution of tert-butyl {(3R)-1-[2-(2-chlorobenzyl)-4,4-dimethoxy-1-(methylthio)-3-oxobut-1-en-1-yl]piperidin-3-yl}carbamate (8.87 g) in N,N-dimethylformamide (90 ml), and the resulting mixture  
15 was stirred at 100°C for 2 hours. The reaction mixture was allowed to cool and water (500 ml) was added thereto, followed by two runs of extraction with ethyl acetate (300 ml). The combined organic layer was concentrated under reduced pressure. The resulting  
20 residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 1/1) to obtain the title compound (7.40 g).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 9.90 (bs, 1H), 7.38–7.36 (m, 1H), 7.18–7.13 (m, 2H), 7.05–7.03 (m, 1H), 5.33 (s, 1H), 4.92–4.90 (m, 1H), 3.92 (s, 2H), 3.77–3.75 (m, 1H), 3.28 (s, 3H), 3.26 (s, 3H), 3.12–3.10 (m, 1H),  
 5 3.00–2.97 (m, 2H), 2.78–2.76 (m, 1H), 1.58–1.49 (m, 4H), 1.43 (s, 9H).

MS (ESI+) 465 ( $\text{M}^+ + 1$ , 56%).

#### Reference Example 49

tert-Butyl {(3R)-1-[4-(2-chloro-5-  
 10 fluorobenzyl)-3-(dimethoxymethyl)-1H-pyrazol-5-yl]piperidin-3-yl}carbamate



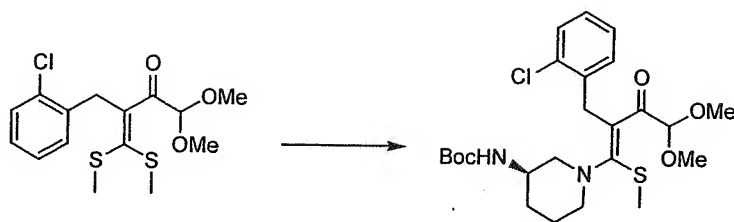
The title compound (22 g) was synthesized by the same process as in Reference Example 48.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.35–7.29 (m, 1H), 6.88–  
 15 6.78 (m, 1H), 6.76–6.73 (m, 1H), 5.34 (s, 1H), 3.88 (s, 2H), 3.80–3.74 (m, 1H), 3.26 (s, 3H), 3.24 (s, 3H), 2.98–2.80 (m, 3H), 1.70–1.46 (m, 5H), 1.42 (s, 9H).  
 MS (ESI+) 483 ( $\text{M}^+ + 1$ , 47%).

#### Reference Example 50

20 tert-Butyl {(3R)-1-[2-(2-chlorobenzyl)-4,4-dimethoxy-1-(methylthio)-3-oxobut-1-en-1-yl]piperidin-

3-yl}carbamate



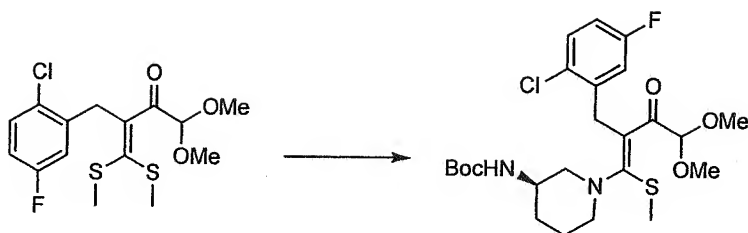
To a solution of 3-(2-chlorobenzyl)-1,1-dimethoxy-4,4-bis(methylthio)but-3-en-2-one (30.4 g) in xylene (220 ml) was added (R)-tert-3-butylpiperidin-3-yl carbamate (21.0 g), and the resulting mixture was heated under reflux for 4 hours. The reaction mixture was allowed to cool, and purified by a silica gel column chromatography (hexane/ethyl acetate = 1/2) to obtain the title compound (8.87 g).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.36-7.34 (m, 1H), 7.17-7.06 (m, 2H), 4.62-4.59 (m, 1H), 4.58 (s, 1H), 4.10-4.08 (m, 2H), 3.70-3.63 (m, 2H), 3.33-3.30 (m, 1H), 3.29 (s, 3H), 3.26 (s, 3H), 3.09-3.07 (m, 1H), 2.84-2.79 (m, 2H), 2.30 (s, 3H), 2.04-1.99 (m, 1H), 1.85-1.81 (m, 1H), 1.64-1.61 (m, 2H), 1.48 (s, 9H).

MS (ESI+) 499 (M<sup>+</sup>+1, 100%).

## Reference Example 51

tert-Butyl {(3R)-1-[(1Z)-2-(2-chloro-5-fluorobenzyl)-4,4-dimethoxy-1-(methylthio)-3-oxobut-1-en-1-yl]piperidin-3-yl}carbamate



The title compound (18.2 g) was synthesized by the same process as in Reference Example 50.

MS (ESI+) 517 ( $M^+ + 1$ , 100%).

#### Reference Example 52

- 5                    3-(2-Chlorobenzyl)-1,1-dimethoxy-4,4-bis(methylthio)but-3-en-2-one



- Tetrahydrofuran (210 ml) and hexamethylphosphoramide (39.1 g) were added to a potassium bis(trimethylsilyl)amide solution (toluene, 15%, 350 ml), and the resulting mixture was stirred at  $-78^{\circ}\text{C}$  for 40 minutes. A solution of 4-(2-chlorophenyl)-1,1-dimethoxybutan-2-one (50.5 g) in tetrahydrofuran (50 ml) was added dropwise thereto over a period of 50 minutes. The resulting mixture was stirred at  $-78^{\circ}\text{C}$  for 20 minutes and carbon disulfide (16.6 g) was added thereto. The reaction mixture was warmed to  $0^{\circ}\text{C}$  over a period of 80 minutes and then stirred under ice-cooling for 30 minutes. The reaction mixture was cooled to

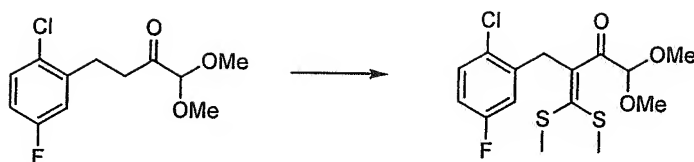
-78°C again and a potassium bis(trimethylsilyl)amide solution (toluene, 15%, 350 ml) was added dropwise thereto over a period of 30 minutes. The resulting mixture was stirred at -78°C for 30 minutes and methyl iodide (28.5 ml) was added thereto. The reaction mixture was warmed to room temperature over a period of 100 minutes and stirred at room temperature for 30 minutes. A saturated aqueous ammonium chloride solution (200 ml) was added thereto and the tetrahydrofuran was distilled off under reduced pressure. Water (500 ml) was added to the residue, followed by two runs of extraction with ethyl acetate (500 ml), and the combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 8/1) to obtain the title compound (36.6 g).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.34-7.32 (m, 1H), 7.19-7.14 (m, 3H), 5.00 (s, 1H), 4.11 (s, 2H), 3.24 (s, 6H), 2.35 (s, 3H), 2.34 (s, 3H).

MS (ESI+) 347 (M<sup>+</sup>+1, 5%).

#### Reference Example 53

3-(2-Chloro-5-fluorobenzyl)-1,1-dimethoxy-4,4-bis(methylthio)but-3-en-2-one



The title compound (34.3 g) was synthesized by the same process as in Reference Example 52.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 7.30-7.26 (m, 1H), 7.01-6.95 (m, 1H), 6.89-6.83 (m, 1H), 5.10 (s, 1H), 4.05 (s, 2H), 3.29 (s, 6H), 2.37 (s, 3H), 2.35 (s, 3H).

MS (ESI+) 365 ( $\text{M}^+ + 1$ , 11%).

#### Reference Example 54

##### 4-(2-Chlorophenyl)-1,1-dimethoxybutan-2-one



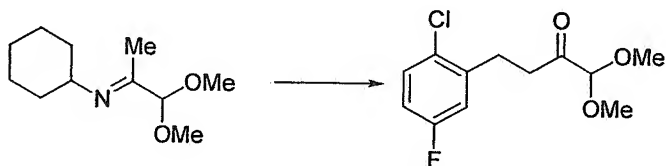
Tetrahydrofuran (200 ml) was added to a lithium diisopropylamide solution (heptane, 2.0 M, 200 ml) at  $-78^\circ\text{C}$  and a solution of N-(2,2-dimethoxy-1-methylethylidene)cyclohexanamine (72.4 g) in tetrahydrofuran (360 ml) was added dropwise thereto over a period of 30 minutes. The resulting mixture was stirred at  $-78^\circ\text{C}$  for 1 hour and 2-chlorobenzyl bromide (82.2 g) was added dropwise thereto over a period of 20 minutes. The reaction mixture was warmed to room temperature over a period of 3 hours. The reaction mixture was cooled to  $0^\circ\text{C}$  and 3N-hydrochloric acid (290

ml) was added thereto and vigorously stirred. The reaction mixture was adjusted to pH 8 with a 5% aqueous potassium carbonate solution and the tetrahydrofuran was distilled off under reduced pressure. The residue was extracted twice with ethyl acetate (500 ml) and the combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 10/1) to obtain the title compound (62.4 g).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.34-7.32 (m, 1H), 7.26-7.24 (m, 1H), 7.17-7.14 (m, 2H), 4.47 (s, 1H), 3.39 (s, 6H), 3.03-2.98 (m, 2H), 2.93-2.89 (m, 2H).

## Reference Example 55

4-(2-Chloro-5-fluorophenyl)-1,1-dimethoxybutan-2-one



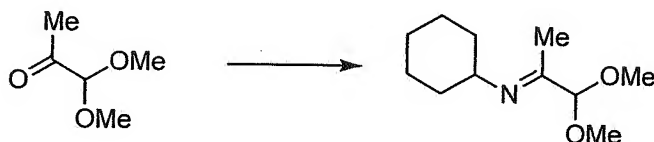
The title compound (38 g) was synthesized by the same process as in Reference Example 54.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.32-7.25 (m, 1H), 7.01-6.97 (m, 1H), 6.89-6.80 (m, 1H), 4.47 (s, 1H), 3.58 (s, 6H), 3.01-2.96 (m, 2H), 2.93-2.87 (m, 2H).

MS (ESI+) 261 (M<sup>+</sup>+1, 19%).

## Reference Example 56

N-(2,2-Dimethoxy-1-methylethylidene)cyclohexaneamine

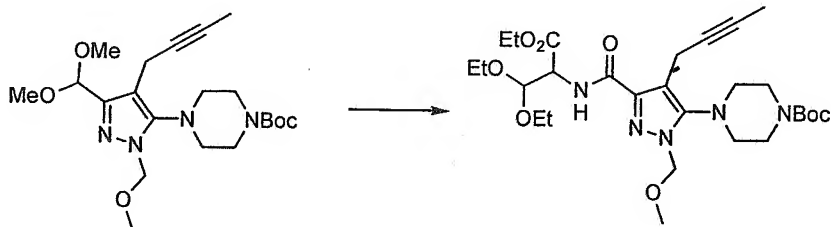


Molecular sieves (4Å, 28 g) and cyclohexylamine (35.2 ml) were added to a solution of pyruvic aldehyde dimethyl acetal (28.0 g) in dichloromethane (237 ml), and the resulting mixture was stirred overnight at room temperature. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to obtain the title compound as a crude product (48.4 g).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 4.43 (s, 1H), 3.39 (s, 6H), 3.38-3.32 (m, 1H), 1.83 (s, 3H), 1.81-1.77 (m, 2H), 1.7.-1.60 (m, 4H), 1.47-1.45 (m, 2H) 1.42-1.28 (m, 2H).

Reference Example 57

tert-Butyl 4-[4-but-2-yn-1-yl-3-([1-diethoxymethyl]-2-ethoxy-2-oxoethyl)amino)carbonyl]-1-(methoxymethyl)-1H-pyrazol-5-yl]pyrazol-5-yl]piperazine-1-carboxylate



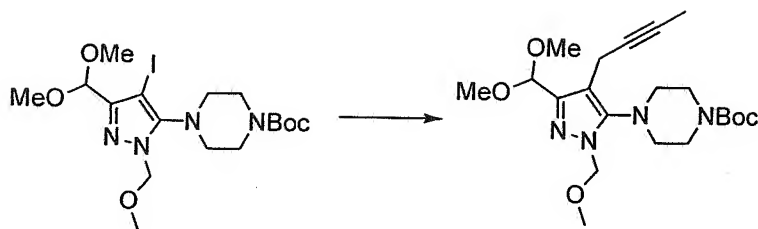
To an ice-cooled solution of tert-butyl 4-[3-(dimethoxy)-4-iodo-1-(methoxymethyl)-1H-pyrazol-5-yl]piperazine-1-carboxylate (400 mg) in dimethylformamide (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (586 mg), 1-hydroxybenzotriazole monohydrate (413 mg) and ethyl 3-ethoxy-O-ethylserinate (627 mg), and the resulting mixture was stirred overnight at room temperature. Water was added to the reaction solution, followed by extraction with ethyl acetate, and the combined organic layer was concentrated under reduced pressure to obtain a crude product. The crude product was purified by a silica gel column chromatography (from chloroform to hexane/ethyl acetate = 2/1 to 1/1) to obtain the title compound (360 mg).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 5.58-5.48 (m, 2H), 5.06-5.03 (m, 1H), 4.87-4.86 (m, 1H), 4.25-4.23 (m, 2H), 3.82-3.74 (m, 2H), 3.68-3.60 (m, 2H), 3.56-3.53 (m, 4H), 3.45-3.33 (m, 2H), 3.38 (s, 3H), 3.15-3.12 (m, 4H), 1.78 (s, 3H), 1.48 (s, 9H), 1.27-1.16 (m, 9H).

MS (ESI+) 580 (M<sup>+</sup>+1, 100%).

#### Reference Example 58

tert-Butyl 4-[4-but-2-yn-1-yl-3-(diethoxymethyl)-1-(methoxymethyl)-1H-pyrazol-5-yl]piperazine-1-carboxylate



A solution of tert-butyl 4-[3-(dimethoxymethyl)-4-iodo-1-(methoxymethyl)-1H-pyrazol-5-yl]piperazine-1-carboxylate (2.50 g) in tetrahydrofuran (50 ml) was cooled to  $-40^{\circ}\text{C}$ , followed by adding dropwise thereto 2N isopropylmagnesium chloride (a tetrahydrofuran solution) (25 ml), and the resulting mixture was stirred at  $-40^{\circ}\text{C}$  for 1 hour. A 1M solution of copper(I) cyanide•lithium chloride in tetrahydrofuran (66 ml) was added to the reaction solution and the resulting mixture was stirred at  $-20^{\circ}\text{C}$  or lower for 30 minutes. After 2-butyne-1-ol (13.3 g) was added dropwise thereto, the resulting mixture was stirred at  $-20^{\circ}\text{C}$  for one and a half hours. The reaction mixture was quenched with methanol and then concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The combined organic layer was concentrated under reduced pressure and the residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 2/1) to obtain the title compound (1.18 g).

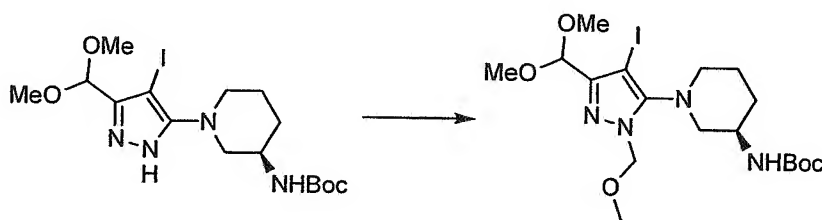
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 5.55 (s, 1H), 5.34 (s, 2H), 3.55-3.52 (m, 4H), 3.38 (s, 6H), 3.37-3.36 (m, 2H), 3.34 (s, 3H), 3.33-3.10 (m, 4H), 1.76-1.74 (m,

3H), 1.47 (s. 9H).

MS (ESI+) 423 ( $M^+ + 1$ , 100%).

# Reference Example 59

tert-Butyl {(3R)-1-[3-(dimethoxymethyl)-4-iodo-1H-pyrazol-5-yl]piperidin-3-yl}carbamate



To a solution of tert-butyl {(3R)-1-[3-(dimethoxymethyl)-4-iodo-1H-pyrazol-5-yl]piperidin-3-yl}carbamate (4.66 g) in N,N-dimethylformamide (20 ml) was added 55% sodium hydride (500.0 mg) at 0°C, and stirred for 20 minutes, followed by adding thereto chloromethyl methyl ether (885.6 mg), and the resulting mixture was stirred at 0°C for 2 hours and then at room temperature for 2 hours. A 10% aqueous potassium hydrogensulfate solution (200 ml) was added to the reaction solution and organic substances were extracted twice therefrom with ethyl acetate (200 ml). The combined organic layer was washed with water (200 ml) and then a saturated aqueous sodium chloride solution (200 ml), dried over anhydrous magnesium sulfate, and then filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified

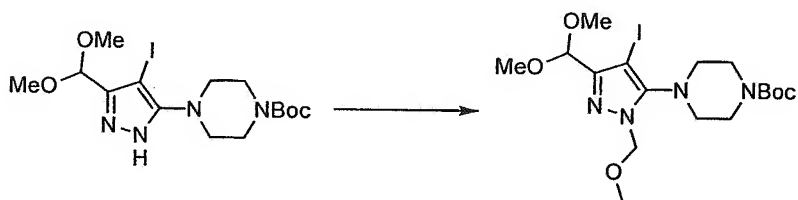
by a silica gel column chromatography (hexane/ethyl acetate = 10/1 to 1/1) to obtain the title compound (3.39 g).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 5.41 (s, 2H), 5.37 (s, 1H), 5.28 (bs, 1H), 3.90-3.84 (m, 1H), 3.42 (s, 6H), 3.38 (s, 3H), 3.25-2.95 (m, 4H), 1.93-1.58 (m, 4H), 1.45 (s, 9H).

MS (ESI+) 511 (M<sup>+</sup>+1, 100%).

#### Reference Example 60

10                   tert-Butyl 4-[3-(dimethoxymethyl)-4-iodo-1-(methoxymethyl)-1H-pyrazol-5-yl]piperazine-1-carboxylate



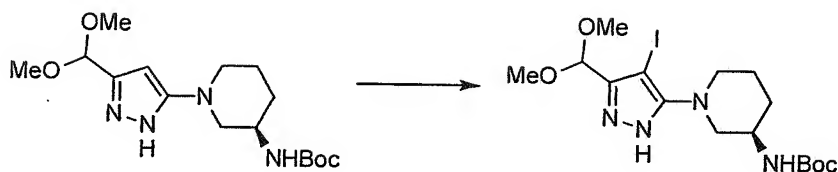
The title compound (3.44 g) was synthesized by the same process as in Reference Example 59.

15   <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 5.41 (s, 2H), 5.37 (s, 1H), 3.56 (t, J = 5.1Hz, 4H), 3.43 (s, 6H), 3.38 (s, 3H), 3.16 (t, J = 5.1Hz, 4H), 1.47 (s, 9H).

MS (ESI+) 497 (M<sup>+</sup>+1, 100%).

#### Reference Example 61

20                   tert-Butyl {(3R)-1-[3-(dimethoxymethyl)-4-iodo-1H-pyrazol-5-yl]piperidin-3-yl}carbamate



Anhydrous potassium carbonate (2.00 g) and iodine (3.40 g) were added to a solution of tert-butyl {(3R)-1-[3-(dimethoxymethyl)-1H-pyrazol-5-yl]piperidin-3-yl}carbamate (4.40 g) in chloroform (50 ml), and the resulting mixture was stirred at room temperature for 3 hours. A 1M aqueous potassium hydrogensulfite solution (200 ml) was added to the reaction solution and organic substances were extracted twice therefrom with chloroform (200 ml). The combined organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain the title compound (6.44 g).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 5.39 (s, 1H), 5.20 (bs, 1H), 3.90-3.84 (m, 1H), 3.31 (s, 6H), 3.25-2.95 (m, 4H), 1.85-1.55 (m, 4H), 1.43 (s, 9H).

MS (ESI+) 467 ( $\text{M}^++1$ , 100%).

#### Reference Example 62

tert-Butyl 4-[3-(dimethoxymethyl)-4-iodo-1H-pyrazol-5-yl]piperazine-1-carboxylate



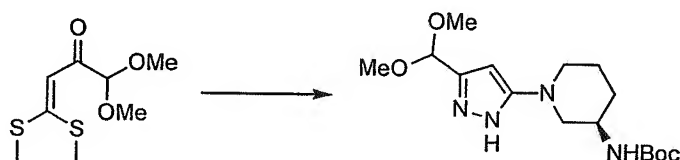
The title compound (10.14 g) was synthesized by the same process as in Reference Example 61.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 5.42 (s, 1H), 3.57 (t,  $J$  = 5.1Hz, 4H), 3.34 (s, 6H), 3.17 (t,  $J$  = 5.1Hz, 4H), 1.48 (s, 9H).

MS (ESI+) 453 ( $M^+ + 1$ , 100%).

#### Reference Example 63

tert-Butyl {(3R)-1-[3-(dimethoxymethyl)-1H-pyrazol-5-yl]piperidin-3-yl}carbamate



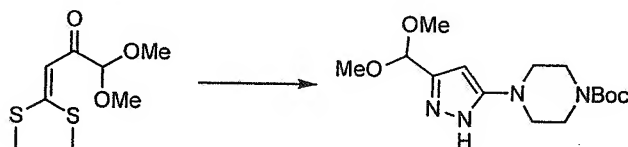
To a solution of 1,1-dimethoxy-4,4-bis(methylthio)-3-buten-2-one (25.0 g) in ethanol (300 ml) was added (R)-tert-3-butylpiperidin-3-yl carbamate (24.0 g), and the resulting mixture was stirred with heating under reflux for 10 hours. After the reaction solution was cooled to room temperature, a solution of hydrazine monohydrate (12.0 g) in ethanol (50 ml) was added thereto, and the resulting mixture was stirred with heating under reflux for 4 hours. The reaction solution was concentrated under reduced pressure and the resulting residue was diluted with and dissolved in chloroform (500 ml). The resulting solution was washed with water (500 ml), dried over anhydrous sodium sulfate and then filtered, and the filtrate was

concentrated under reduced pressure. To the resulting residue was added chloroform (500 ml) and the residue was dissolved with heating under reflux. After hexane (250 ml) was added thereto, the resulting mixture was stirred for 1 hour while being cooled to 0°C, and the solid precipitated was collected by filtration to obtain the title compound (9.52 g).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 5.71 (s, 1H), 5.47 (s, 1H), 4.85 (bs, 1H), 3.85-3.70 (m, 1H), 3.31 (s, 6H), 3.25-2.95 (m, 4H), 1.85-1.50 (m, 4H), 1.42 (s, 9H).  
MS (ESI+) 341 (M<sup>+</sup>+1, 100%).

#### Reference Example 64

tert-Butyl 4-[3-(dimethoxymethyl)-1H-pyrazol-5-yl]piperazine-1-carboxylate

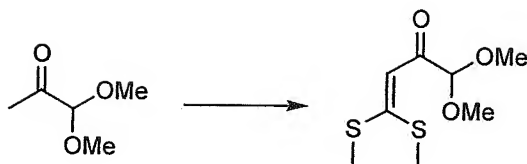


The title compound (16.10 g) was synthesized by the same process as in Reference Example 63.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 5.74 (s, 1H), 5.50 (s, 1H), 3.55 (t, J = 5.1Hz, 4H), 3.33 (s, 6H), 3.16 (t, J = 5.1Hz, 4H), 1.48 (s, 9H).  
MS (ESI+) 327 (M<sup>+</sup>+1, 100%).

#### Reference Example 65

1,1-Dimethoxy-4,4-bis(methylthio)-3-buten-2-one



Carbon disulfide (7.61 g) was added to a suspension of 55% sodium hydride (9.60 g) in dimethylformamide (250 ml) at 0°C over a period of 10 minutes and stirred for 30 minutes, and then a solution  
 5 of 1,1-dimethoxyacetone (11.8 g) in N,N-dimethylformamide (50 ml) was added thereto over a period of 30 minutes. An ice bath was removed, followed by stirring with warming for 2 hours. After tetrahydrofuran (200 ml) was added to the reaction  
 10 solution, the resulting mixture was cooled to 0°C and then a solution of iodomethane (35.5 g) in tetrahydrofuran (50 ml) was added thereto over a period of 30 minutes. An ice bath was removed and the reaction solution was stirred for 1 hour while being  
 15 warmed to room temperature. A 10% aqueous potassium hydrogensulfate solution (500 ml) was added to the reaction solution and organic substances were extracted twice therefrom with ethyl acetate (500 ml). The combined organic layer was washed with water (500 ml)  
 20 and then a saturated aqueous sodium chloride solution (500 ml), dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure to obtain the title compound (25.0 g).  
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 6.34 (s, 1H), 4.53 (s,

1H), 3.38 (s, 6H), 2.46 (s, 6H).

#### Reference Example 66

##### Methyl 2-amino-3-oxobutanoate hydrochloride



A 10% palladium-active carbon carrier

- 5 (containing 50% water, 0.60 g) and a 10% solution of hydrochloric acid in methanol (15 ml) were added to a solution of methyl 2-(hydroxyimino)-3-oxobutanoate (3.00 g) in methanol (15 ml), and the resulting mixture was stirred for 2 hours at room temperature under a
- 10 hydrogen atmosphere at atmospheric pressure and then treated with nitrogen to replace the air. The palladium-active carbon carrier was filtered off and the filtrate was concentrated under reduced pressure to obtain the title compound (3.46 g).
- 15 <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 8.90 (bs, 3H), 5.31 (s, 1H), 3.81 (s, 3H), 2.38 (s, 3H).

#### Reference Example 67

##### Methyl 2-(hydroxyimino)-3-oxobutanoate

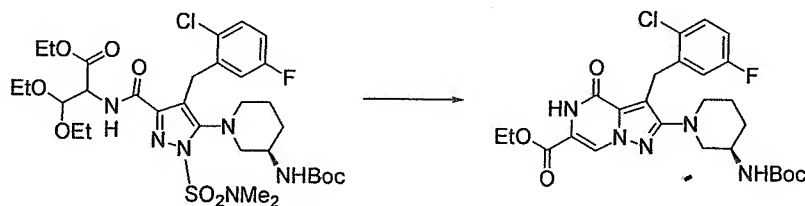


An aqueous solution (30 ml) of sodium nitrite (16.3 g) was added to a solution of methyl acetoacetate (25.0 g) in acetic acid (100 ml) over a period of 1 hour while maintaining the internal temperature at 12°C or lower, and the resulting mixture was stirred overnight while being slowly warmed to room temperature. The reaction solution was diluted with water (1000 ml) and sodium hydrogencarbonate was added thereto with stirring until no more foaming was observed. Organic substances were extracted twice therefrom with ethyl acetate (500 ml) and the combined organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain the title compound (20.3 g).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 10.00 (bs, 1H), 3.91 (s, 3H), 2.42 (s, 3H).

## Reference Example 68

Ethyl 2-[(3R)-3-[(tert-butoxycarbonyl)amino]-piperidin-1-yl]-3-(2-chloro-5-fluorobenzyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-6-carboxylate



Water (20 ml) and a 4N hydrochloric acid/1,4-

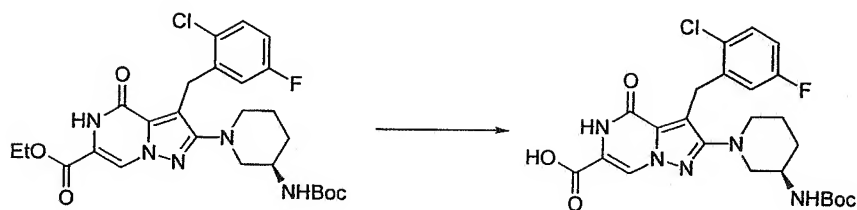
dioxane solution (40 ml) were added to a solution of ethyl N-({5-((3R)-3-[(tert-butoxycarbonyl)aminopiperidin-1-yl]-4-(2-chloro-5-fluorobenzyl)-1-[(dimethylamino)sulfonyl]-1H-pyrazol-3-yl}carbonyl)-3-ethoxy-O-ethylserinate (1.50 g) in 1,4-dioxane (20 ml), and the resulting mixture was stirred at 50°C for 2 hours. The reaction solution was cooled to 0°C and 1,4-dioxane (30 ml), water (20 ml) and sodium hydrogencarbonate (30 g) were added thereto.

The resulting mixture was warmed to room temperature and di-tert-butyl dicarbonate (1.61 g) was added thereto and stirred overnight. 1,4-Dioxane was distilled off under reduced pressure and water (100 ml) was added to the residue, followed by two runs of extraction with ethyl acetate (100 ml). The combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 2/1) to obtain the title compound (630 mg).

MS (ESI+) 448 ( $M^+ + 1$ , 30%).

## Reference Example 69

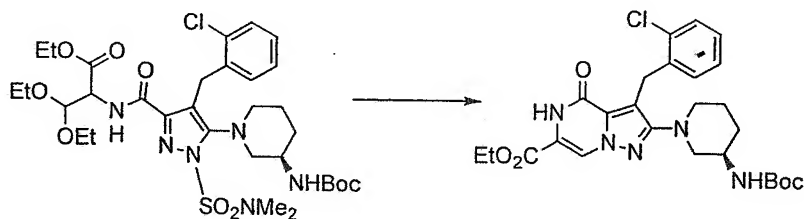
2-((3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl)-3-(2-chloro-5-fluorobenzyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-6-carboxylic acid



A solution consisting of ethyl 2-((3R)-3-  
 [(tert-butoxycarbonyl)amino]piperidin-1-yl)-3-(2-  
 chloro-5-fluorobenzyl)-4-oxo-4,5-dihydropyrazolo[1,5-  
 a]pyrazin-6-carboxylate (630 mg), ethanol (10 ml) and a  
 5 1N aqueous sodium hydroxide solution (10 ml) was  
 stirred at 80°C for 1 hour. The reaction solution was  
 allowed to cool, adjusted to pH 6 with a saturated  
 aqueous ammonium chloride solution, and then extracted  
 with ethyl acetate. The organic layer was washed with  
 10 a saturated aqueous sodium chloride solution, dried  
 over sodium sulfate and then filtered, and the filtrate  
 was concentrated under reduced pressure to obtain the  
 title compound (580 mg).  
 MS (ESI+) 520 ( $M^+ + 1$ , 33%).

#### 15 Reference Example 70

Ethyl 2-((3R)-3-[(tert-butoxycarbonyl)amino]-  
 piperidin-1-yl)-3-(2-chlorobenzyl)-4-oxo-4,5-dihydro-  
 pyrazolo[1,5-a]pyrazin-6-carboxylate

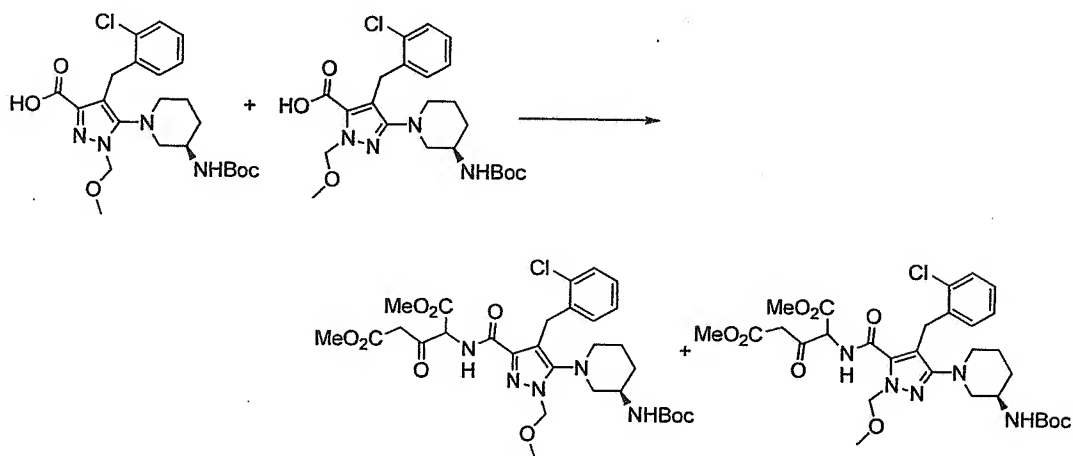


Water (20 ml) and a 4N hydrochloric acid/1,4-dioxane solution (40 ml) were added to a solution of ethyl N-({5-((3R)-3-[(tert-butoxycarbonyl)aminopiperidin-1-yl]-4-(2-chlorobenzyl)-1-[(dimethylamino)sulfonyl]-1H-pyrazol-3-yl}carbonyl)-3-ethoxy-O-ethylserinate (2.69 g) in 1,4-dioxane (20 ml), and the resulting mixture was stirred at 50°C for 2 hours. The reaction solution was cooled to 0°C and 1,4-dioxane (30 ml), water (20 ml) and sodium hydrogen-  
10 carbonate (30 g) were added thereto. The resulting mixture was warmed to room temperature and di-tert-butyl dicarbonate (1.61 g) was added thereto and stirred overnight. The 1,4-dioxane was distilled off under reduced pressure and water (100 ml) was added to  
15 the residue, followed by two runs of extraction with ethyl acetate (100 ml). The combined organic layer was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 2/1) to obtain  
20 the title compound (1.03 g).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 8.47 (bs, 1H), 8.06 (s, 1H), 7.40-7.3 (m, 1H), 7.18-7.13 (m, 2H), 6.98-6.96 (m, 1H), 4.65-4.37 (m, 5H), 3.73-3.71 (m, 1H), 3.27-3.24 (m, 1H), 3.06-3.02 (m, 2H), 2.88-2.85 (m, 1H), 1.53-  
25 1.48 (m, 4H), 1.44 (s, 9H), 1.40 (t, J = 7.2Hz, 3H).  
MS (ESI+) 530 (M<sup>+</sup>+1, 52%).

Reference Example 71

Dimethyl N-{[5-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazol-3-yl]carbonyl}-3-oxoglutamate mixture



5 N-methylmorpholine (105.6 mg) and isobutyl chlorocarbonate (142.6 mg) were added to a solution of a 5-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazole-3-carboxylic acid mixture (500.0 mg) in tetrahydrofuran  
 10 (10 ml), and the resulting mixture was stirred at  $-20^{\circ}\text{C}$  for 30 minutes. Then, dimethyl 3-oxoglutamate hydrochloride (300.0 mg) was added thereto, followed by adding dropwise thereto N-methylmorpholine (134.5 mg) slowly, and the resulting mixture was stirred overnight  
 15 while being slowly warmed from  $-20^{\circ}\text{C}$  to room temperature. A 10% aqueous potassium hydrogensulfate solution (50 ml) was added to the reaction solution and organic substances were extracted twice therefrom with ethyl acetate (30 ml). The combined organic layer was

washed with a saturated aqueous sodium chloride solution (50 ml), dried over anhydrous magnesium sulfate and then filtered, and the filtrate was concentrated under reduced pressure. The resulting  
 5 residue was purified by a silica gel thin-layer chromatography (hexane/ethyl acetate = 1/1) to obtain the title compound (57.5 mg).  
 MS (ESI+) 650 ( $M^+ + 1$ , 100%).

## Reference Example 72

10 Dimethyl 3-oxoglutamate hydrochloride



A 10% palladium-active carbon carrier (containing 50% water, 0.30 g) and a 10% solution of hydrochloric acid in methanol (5 ml) were added to a solution of dimethyl 2-(hydroxyimino)-3-oxopentanedioate (1.26 g) in methanol (5 ml), and the  
 15 resulting mixture was stirred for 2 hours at room temperature under a hydrogen atmosphere at atmospheric pressure and then treated with nitrogen to replace the air. The palladium-active carbon carrier was filtered  
 20 off and the filtrate was concentrated under reduced pressure to obtain the title compound (1.40 g).  
 $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  ppm 9.03 (bs, 3H), 5.46 (bs, 1H), 4.03 (d,  $J$  = 16.8Hz, 1H), 3.92 (d,  $J$  = 16.8Hz,

1H), 3.77 (s, 3H), 3.64 (s, 3H).

### Reference Example 73

Dimethyl 2-(hydroxyimino)-3-oxopentanedioate

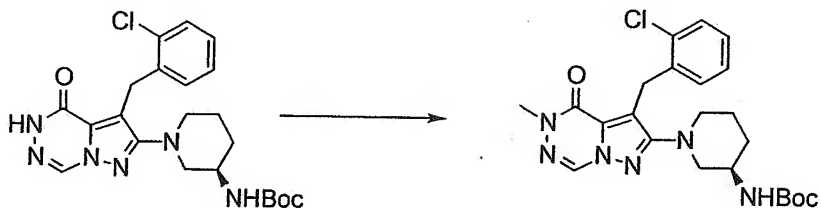


Chlorotrimethylsilane (1.20 g) and then  
 5 isopentyl nitrite (1.40 g) were added to a solution of  
 dimethyl 3-oxopentanedioate (1.74 g) in dichloromethane  
 (5 ml) while maintaining the internal temperature at  
 -20°C or lower, and the resulting mixture was stirred  
 for 3 hours while being slowly warmed to room  
 10 temperature. An aqueous sodium hydrogencarbonate  
 solution (50 ml) was added to the reaction solution and  
 organic substances were extracted twice therefrom with  
 ethyl acetate (30 ml). The combined organic layer was  
 dried over anhydrous sodium sulfate and then  
 15 concentrated under reduced pressure. The resulting  
 residue was purified by a silica gel column  
 chromatography (hexane/ethyl acetate = 4/1) to obtain  
 the title compound (1.26 g).  
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm 10.37 (bs, 1H), 3.92 (s,  
 20 3H), 3.84 (s, 2H), 3.76 (s, 3H).

### Reference Example 74

tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-5-

methyl-4-oxo-4,5-dihydropyrazolo[1,5-d][1,2,4]triazin-2-yl]piperidin-3-yl} carbamate

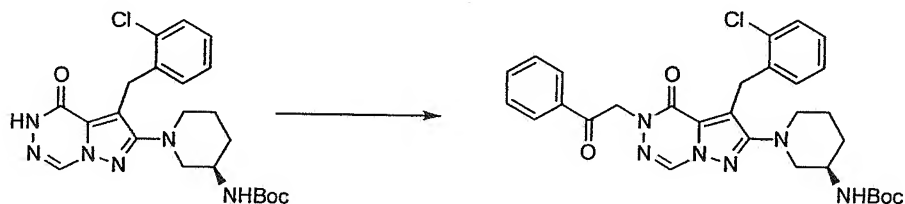


The title compound (87 mg) was synthesized by the same process as in Reference Example 17.

5 MS (ESI+) 473 ( $M^+ + 1$ , 100%).

#### Reference Example 75

tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydropyrazolo[1,5-d][1,2,4]triazin-2-yl]piperidin-3-yl} carbamate

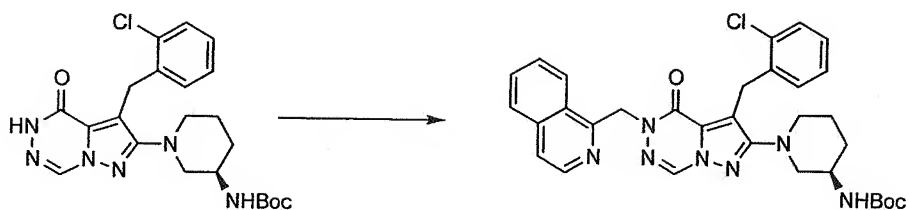


10 The title compound (131 mg) was synthesized by the same process as in Reference Example 12.

MS (ESI+) 577 ( $M^+ + 1$ , 100%).

#### Reference Example 76

15 tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-5-(isoquinolin-1-ylmethyl)-4-oxo-4,5-dihydropyrazolo[1,5-d][1,2,4]triazin-2-yl]piperidin-3-yl} carbamate

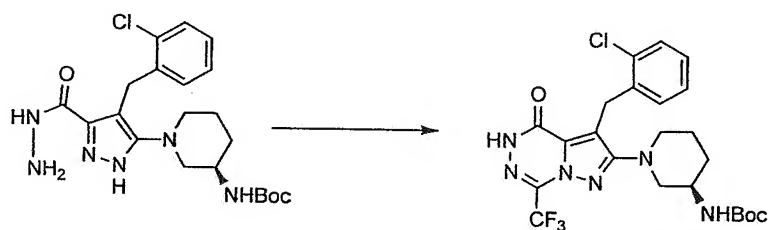


The title compound (122 mg) was synthesized by the same process as in Reference Example 12.

MS (ESI+) 600 ( $M^+ + 1$ , 100%).

#### Reference Example 77

5 tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-4-oxo-7-(trifluoromethyl)-4,5-dihydropyrazolo[1,5-d][1,2,4]triazin-2-yl]piperidin-3-yl}carbamate



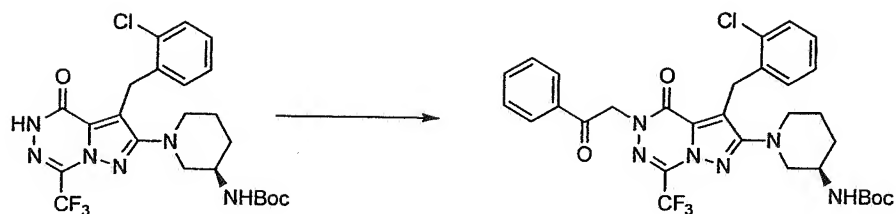
A solution of tert-butyl {(3R)-1-[4-(2-chlorobenzyl)-3-(hydrazinecarbonyl)-1H-pyrazol-5-yl]piperidin-3-yl}carbamate (80 mg) in a mixture of trifluoroacetic acid (0.5 ml) and polyphosphoric acid (2 ml) was stirred with heating at 140°C for 16 hours. The reaction solution was cooled to room temperature, adjusted to pH 10 with a 10% aqueous potassium carbonate solution and then extracted twice with chloroform (50 ml). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate

was concentrated under reduced pressure. To a solution of the resulting residue (70 mg) in tetrahydrofuran (5 ml) were added a saturated aqueous sodium hydrogencarbonate solution (5 ml) and di-tert-butyl dicarbonate (81 mg), and the resulting mixture was stirred overnight at room temperature. After the tetrahydrofuran was distilled off under reduced pressure, a 10% aqueous potassium carbonate solution was added to the residue, followed by extraction with ethyl acetate (100 ml). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by a thin-layer chromatography (silica gel, hexane/ethyl acetate = 3/1) to obtain the title compound (6 mg).

$^1\text{H}$  NMR(300MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 9.58 (bs, 1H), 7.43-7.39 (m, 1H), 7.20-7.17 (m, 2H), 6.96-6.93 (m, 1H), 4.62-4.41 (m, 3H), 3.68-3.66 (m, 1H), 3.31-3.29 (m, 1H), 3.15-2.98 (m, 3H), 1.65-1.48 (m, 4H), 1.44 (s, 9H).  
MS (ESI+) 527 ( $\text{M}^+ + 1$ , 55%).

#### Reference Example 78

tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-4-oxo-5-(2-oxo-2-phenylethyl)-7-(trifluoromethyl)-4,5-dihydropyrazolo[1,5-d][1,2,4]triazin-2-yl]piperidin-3-yl}carbamate

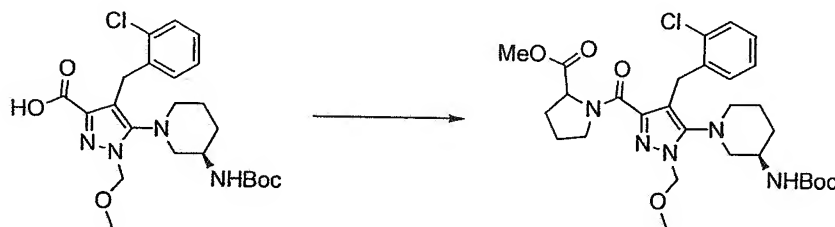


The title compound (21 mg) was synthesized by the same process as in Reference Example 12.

MS (ESI+) 645 ( $M^+ + 1$ , 13%).

#### Reference Example 79

- 5           Methyl 1-{[5-{(3R)-3-[(tert-butoxycarbonyl)-amino]piperidin-1-yl}-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazol-3-yl]carbonyl}pyrrolinate

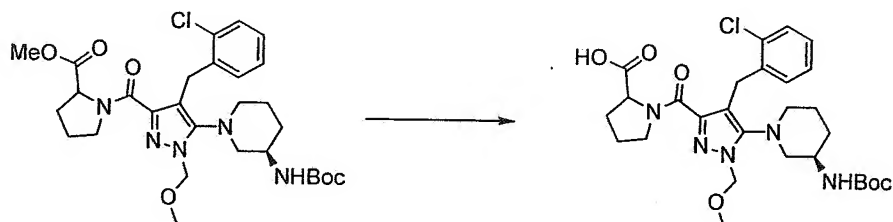


The title compound (810 mg) was synthesized by the same process as in Reference Example 57.

- 10   <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 5.58-5.48 (m, 2H), 5.06-5.03 (m, 1H), 4.87-4.86 (m, 1H), 4.25-4.23 (m, 2H), 3.82-3.74 (m, 2H), 3.68-3.60 (m, 2H), 3.56-3.53 (m, 4H), 3.45-3.33 (m, 2H), 3.38 (s, 3H), 3.15-3.12 (m, 4H), 1.78 (s, 3H), 1.48 (s, 9H), 1.27-1.16 (m, 9H).
- 15   MS (ESI+) 580 ( $M^+ + 1$ , 100%).

#### Reference Example 80

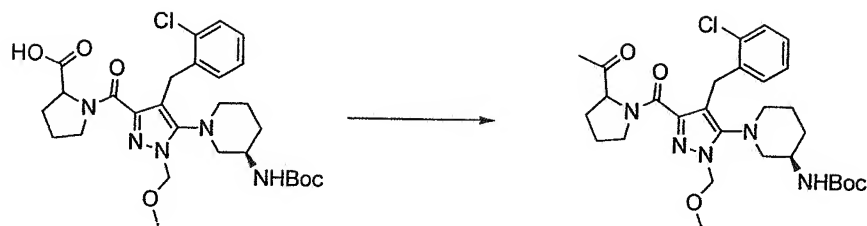
1-([5-((3R)-3-[(tert-butoxycarbonyl)amino]-piperidin-1-yl)-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazolo-3-yl]carbonyl}proline



A 1N-aqueous sodium hydroxide solution (1.0  
 5 ml) was added to a solution of methyl 1-([5-((3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl)-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazolo-3-yl]carbonyl}prolinate (430 mg) in tetrahydrofuran (3.0 ml), and the resulting mixture was stirred at 50°C for  
 10 2 hours. The mixture was cooled to room temperature and a 5% aqueous sodium hydrogensulfate solution (50 ml) was added thereto, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure to obtain the title compound as  
 15 a crude product (718 mg).  
 MS (ESI+) 576 ( $M^+ + 1$ , 73%).

#### Reference Example 81

tert-Butyl {(3R)-1-[3-[(3-acetylpyrrolidin-1-yl)carbonyl]-4-(2-chlorobenzyl)-1-methoxymethyl]-1H-  
 20 pyrazolo-5-yl}piperidin-3-yl}carbamate



To a solution of 1-[[5-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazolo-3-yl]carbonyl]proline (718 mg) in N,N-dimethylformamide (5.0 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (665 mg), 1-hydroxybenzotriazole monohydrate (512 mg) and N,O-dimethylhydroxylamine hydrochloride (243 mg), and the resulting mixture was stirred overnight at room temperature. Water was added to the reaction solution, followed by extraction with ethyl acetate, and the combined organic layer was concentrated under reduced pressure to obtain a crude product. The crude product was purified by a silica gel column chromatography (hexane/ethyl acetate = 2/1 to 1/2) to obtain a product (585 mg). MS (ESI+) 619 ( $M^+ + 1$ , 100%).

Heated and dried cerium chloride (464 mg) and methylmagnesium bromide (4.4 mol) were added to a solution of the product in tetrahydrofuran (5.0 ml) at 0°C, and the resulting mixture was stirred with heating at 50°C for one and a half hours. After the reaction solution was cooled to room temperature, a saturated aqueous ammonium chloride solution was added thereto,

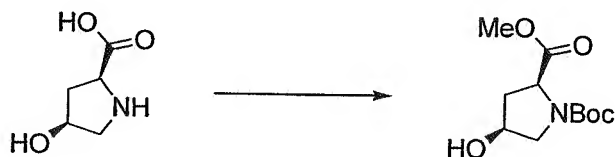
followed by extraction with ethyl acetate. The combined organic layer was concentrated under reduced pressure to obtain a crude product. The crude product was purified by a silica gel column chromatography (chloroform/methanol = 10/1) to obtain the desired title compound (118 mg).

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  ppm 10.74 (s, 1H), 8.23 (bs, 3H), 7.50-7.35 (m, 1H), 7.30-7.05 (m, 2H), 7.05-6.80 (m, 1H), 4.35 (s, 2H), 3.83 (s, 3H), 3.80-3.60 (m, 1H), 3.20-2.90 (m, 2H), 2.75 (s, 3H), 2.65-2.40 (m, 2H), 2.00-1.80 (m, 1H), 1.70-1.20 (m, 3H).

MS (ESI+) 574 ( $M^+ + 1$ , 100%).

#### Reference Example 82

1-tert-Butyl 2-methyl-(2S, 4S)-4-hydroxy-pyrrolidine-1,2-dicarboxylate



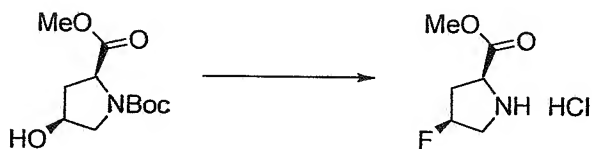
Thionyl chloride (612 ml) was added dropwise to a solution of L-hydroxyproline (1.0 g) in methanol (10 ml) at room temperature, and the resulting mixture was stirred overnight at room temperature. The reaction solution was concentrated under reduced pressure, followed by adding thereto chloroform (10 ml) and a saturated aqueous sodium hydrogencarbonate solution and then di-tert-butyl dicarbonate (2.5 g),

and the resulting mixture was stirred at room temperature for 2 hours. The organic layer was concentrated under reduced pressure to obtain the title compound as a crude product (3.38 g).

- 5  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 5.58-5.48 (m, 2H), 5.06-5.03 (m, 1H), 4.87-4.86 (m, 1H), 4.25-4.23 (m, 2H), 3.82-3.74 (m, 2H), 3.68-3.60 (m, 2H), 3.56-3.53 (m, 4H), 3.45-3.33 (m, 2H), 3.38 (s, 3H), 3.15-3.12 (m, 4H), 1.78 (s, 3H), 1.48 (s, 9H), 1.27-1.16 (m, 9H).
- 10 MS (ESI+) 580 ( $\text{M}^+ + 1$ , 100%).

#### Reference Example 83

Methyl (4S)-4-fluoro-L-prolinate  
hydrochloride



- Diethylamine sulfur=trifluoride (1.4 ml) was
- 15 added to a solution (5.0 ml) of 1-tert-butyl 2-methyl-  
(2S, 4S)-4-hydroxypyrrolidine-1,2-dicarboxylate (2.0 g)  
in dichloromethane at  $-78^\circ\text{C}$ , and the resulting mixture  
was stirred at room temperature for 4 hours. A  
saturated aqueous ammonium chloride solution was added
- 20 to the reaction solution, followed by extraction with  
ethyl acetate, and the combined organic layer was  
concentrated under reduced pressure to obtain a crude  
product. The crude product was purified by a silica

gel column chromatography (chloroform/methanol = 10/1) to obtain a product (1.87 g).

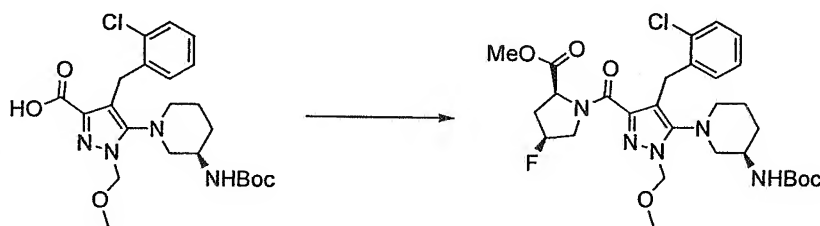
MS (ESI+) 248 ( $M^+ + 1$ , 100%).

To a solution of this product in chloroform was added a 4N hydrochloric acid/1,4-dioxane solution, and the resulting mixture was stirred at room temperature for 3 hours. The reaction solution was concentrated under reduced pressure to obtain the title compound (552 mg).

MS (ESI+) 148 ( $M^+ + 1$ , 100%).

#### Reference Example 84

Methyl (4S)-1-{[5-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazol-3-yl]carbonyl}-4-fluoro-L-prolinate



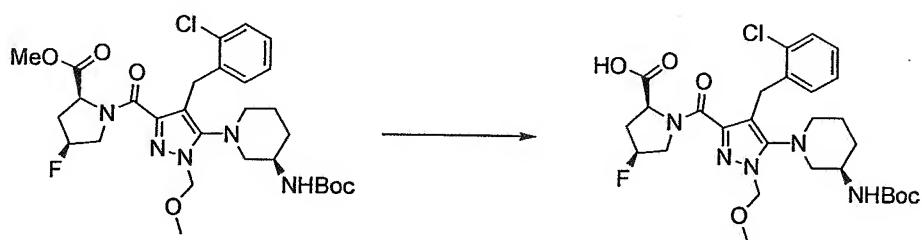
The title compound (810 mg) was synthesized by the same process as in Reference Example 57.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 5.58-5.48 (m, 2H), 5.06-5.03 (m, 1H), 4.87-4.86 (m, 1H), 4.25-4.23 (m, 2H), 3.82-3.74 (m, 2H), 3.68-3.60 (m, 2H), 3.56-3.53 (m, 4H), 3.45-3.33 (m, 2H), 3.38 (s, 3H), 3.15-3.12 (m, 4H), 1.78 (s, 3H), 1.48 (s, 9H), 1.27-1.16 (m, 9H).

MS (ESI+) 580 ( $M^+ + 1$ , 100%).

Reference Example 85

(4S)-1-{{[5-{{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazol-3-yl]carbonyl}-4-fluoro-L-proline

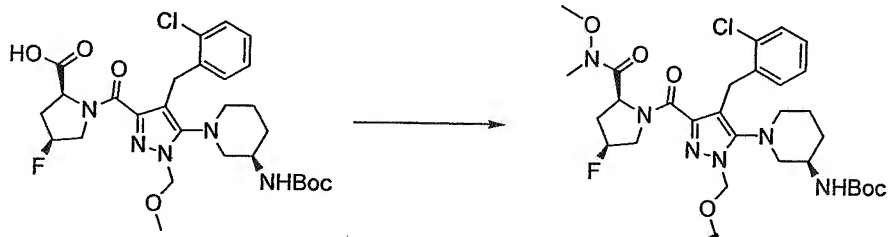


The title compound (810 mg) was synthesized by the same process as in Reference Example 80.

MS (ESI+) 580 ( $M^+ + 1$ , 100%).

10 Reference Example 86

tert-Butyl {(3R)-1-[4-(2-chlorobenzyl)-3-[[((2S,4S)-4-fluoro-2-[[methoxy(methyl)amino]-carbonyl]pyrrolidin-1-yl)carbonyl]-1-(methoxymethyl)-1H-pyrazol-5-yl]piperidin-3-yl}carbamate

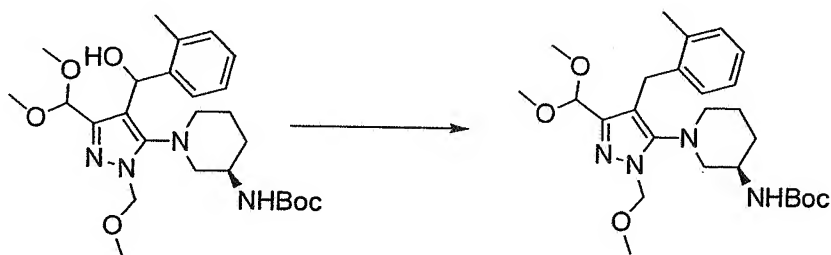


15 The title compound (440 mg) was obtained by the same process as in Reference Example 81.

MS (ESI+) 637 ( $M^+ + 1$ , 30%).

Reference Example 87

tert-Butyl {(3R)-1-[3-(dimethoxymethyl)-1-(methoxymethyl)-4-(2-methylbenzyl)-1H-pyrazolo-5-yl]piperidin-3-yl}carbamate

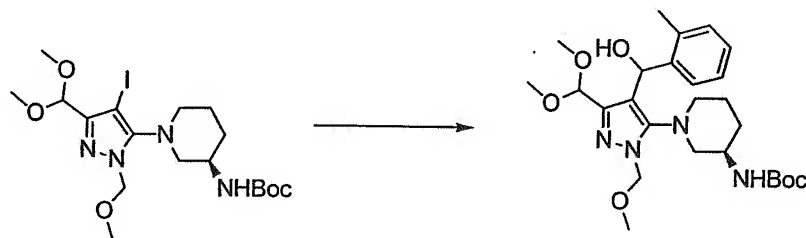


Trifluoroacetic acid (0.1 ml) and triethylsilane (0.32 ml) were added to a solution (1.0 ml) of tert-butyl {(3R)-1-[3-(dimethoxymethyl)-4-[hydroxy(2-methylphenyl)methyl]-1-(methoxymethyl)-1H-pyrazolo-5-yl]piperidin-3-yl}carbamate (50 mg) in dichloromethane, and the resulting mixture was stirred overnight at room temperature. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with chloroform, and the combined organic layer was concentrated under reduced pressure to obtain a crude product. The crude product was purified by a silica gel column chromatography (hexane/ethyl acetate = 2/1) to obtain the title compound (31.5 mg).

MS (ESI+) 487 ( $M^+ + 1$ , 100%).

## Reference Example 88

tert-Butyl {(3R)-1-[3-(dimethoxymethyl)-4-[hydroxy(2-methylphenyl)methyl]-1-(methoxymethyl)-1H-pyrazolo-5-yl]piperidin-3-yl}carbamate

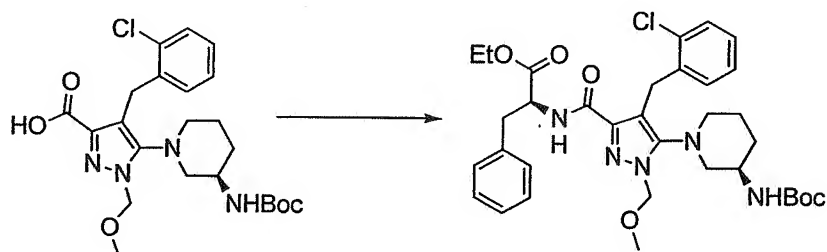


- 5 To a solution (40 ml) of tert-butyl {(3R)-1-[3-(dimethoxymethyl)-4-iodo-1-(methoxymethyl)-1H-pyrazol-5-yl]piperidin-3-yl}carbamate (2.7 g) in tetrahydrofuran was added 2M isopropylmagnesium chloride (27 ml) at -20°C, and stirred for 30 minutes.
- 10 To the reaction solution was added dropwise o-tolualdehyde (7.8 g), and the resulting mixture was warmed to room temperature and then stirred for 3 hours. A saturated aqueous ammonium chloride solution was added to the reaction solution, followed by
- 15 extraction with ethyl acetate, and the combined organic layer was concentrated under reduced pressure to obtain a crude product. The crude product was purified by a silica gel column chromatography (hexane/ethyl acetate = 2/1) to obtain the title compound (1.37 g).
- 20 MS (ESI+) 505 ( $M^+ + 1$ , 100%).

## Reference Example 89

Ethyl N-{[5-{(3R)-3-[(tert-

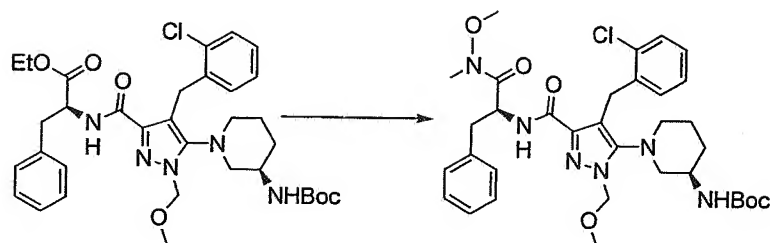
butoxycarbonyl)amino]piperidin-1-yl}-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazol-3-yl]carbonyl}-L-phenylalaninate



The title compound (630 mg) was synthesized  
 5 by the same process as in Reference Example 57.  
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 7.38-7.28 (m, 2H), 7.25-7.18 (m, 2H), 7.17-7.11 (m, 1H), 7.08-7.05 (m, 1H), 6.98-6.95 (m, 1H), 5.45 (d, J = 10.6 Hz, 1H), 5.24 (d, J = 10.6 Hz, 1H), 4.97-4.92 (m, 1H), 4.87-4.82 (m, 1H),  
 10 4.18 (q, J = 7.1 Hz, 2H), 4.07 (d, J = 13.8 Hz, 1H), 4.05 (d, J = 13.8 Hz, 1H), 3.73-3.68 (m, 1H), 3.27 (s, 3H), 3.22-3.15 (m, 1H), 3.08-3.01 (m, 2H), 2.93-2.84 (m, 2H), 2.73-2.65 (m, 1H), 1.60-1.48 (m, 4H), 1.43 (s, 9H), 1.24 (t J = 7.1 Hz, 3H).  
 15 MS (ESI+) 654 (M<sup>+</sup>+1, 100%).

#### Reference Example 90

N-{{5-[(3R)-3-[(tert-butoxycarbonyl)amino]-piperidin-1-yl]-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazol-3-yl]carbonyl}-N-methoxy-N-methyl-L-  
 20 phenylalaninamide

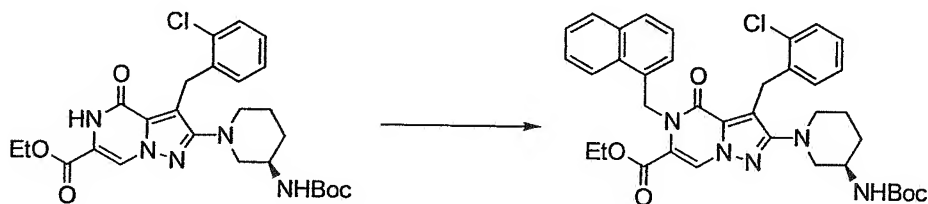


A 1N-aqueous sodium hydroxide solution (1.1 ml) was added to a solution of ethyl N-([5-((3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl)-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazol-3-yl]carbonyl)-L-phenylalaninate (430 mg) in tetrahydrofuran (20 ml), and the resulting mixture was stirred at 50°C for 3 hours. The reaction solution was cooled to room temperature, neutralized with 1N-hydrochloric acid, poured into water (120 ml) and then extracted with ethyl acetate (50 ml x 2). The organic layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. To a solution of N-([5-((3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl)-4-(2-chlorobenzyl)-1-(methoxymethyl)-1H-pyrazol-3-yl]carbonyl)-L-phenylalanine (718 mg) as a crude product in N,N-dimethylformamide (30 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (387 mg), 1-hydroxybenzotriazole monohydrate (272 mg) and N,O-dimethylhydroxylamine hydrochloride (197 mg), and the resulting mixture was stirred at room temperature for 18 hours. The reaction

solution was poured into a saturated aqueous sodium chloride solution (200 ml) and extracted with ethyl acetate (60 ml x 2). The combined organic layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 2/1) to obtain the title compound (200 mg). MS (ESI+) 669 ( $M^+ + 1$ , 38%).

# 10 Reference Example 91

Ethyl 2-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-3-(2-chlorobenzyl)-5-(1-naphthylmethyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-6-carboxylate



15 Sodium iodide (11.3 mg), potassium carbonate (156 mg) and 1-(chloromethyl)naphthalene (0.0847 ml) were added to a solution of ethyl 2-[(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl]-3-(2-chlorobenzyl)-4-oxo-4,5-dihydropyrazolo[1,5-a]pyrazin-6-carboxylate (200 mg) in N,N-dimethylformamide (5.0 ml), and the resulting mixture was stirred overnight at room temperature. Water (50 ml) was added to the

reaction mixture, followed by two runs of extraction with ethyl acetate (50 ml). The combined organic layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under  
5 reduced pressure. The resulting residue was purified by a silica gel column chromatography (hexane/ethyl acetate = 5/1) to obtain the title compound (222 mg). MS (ESI+) 670 ( $M^+ + 1$ , 100%).

In vitro DPP-IV inhibitory effect measurement test

10 Human serum containing DPP-IV enzyme was used in an experiment after being diluted with assay buffer (25mM Tris-HCl, 140mM NaCl, 10mM KCl, pH 7.9) (finally, diluted 10-fold). Each of solutions of each test compound having various concentrations was added to the  
15 diluted serum and the resulting mixture was incubated at room temperature. Then, a substrate (Glycyl-L-Proline 4-Methyl-Coumaryl-7-Amide, Peptide Laboratories Co., Ltd.) was added thereto to a final concentration of 100  $\mu$ M and the reaction was carried out at room  
20 temperature. Acetic acid was added to the reaction mixture to a final concentration of 12.5% to terminate the reaction, and the intensity of fluorescence at an excitation wavelength of 360 nm and a measuring wavelength of 460 nm was measured by the use of a  
25 fluorescent plate reader. A compound concentration for 50% inhibition was calculated as an  $IC_{50}$  value from enzyme inhibitory activity values obtained by adding

each test compound to a plurality of concentrations.

Table 1

Test Compound	Inhibitory activity against human DPP IV IC <sub>50</sub> (nM)
Example 1	20
Example 3	30
Example 4	37
Example 5	82
Example 7	0.7
Example 8	7.0
Example 9	71
Example 10	2.8
Example 11	25
Example 12	24
Example 13	6.1
Example 14	61
Example 16	2.5
Example 17	1.6
Example 18	45
Example 19	15
Example 20	5.0
Example 21	13
Example 26	28
Example 32	0.9
Example 33	12
Example 34	2.8
Example 35	2.3
Example 38	9.6
Example 41	2.1

#### INDUSTRIAL APPLICABILITY

The present invention makes it possible to provide compounds having DPP-IV inhibitory activity and improved in safety, nontoxicity and the like.

The present inventive compounds are useful for the suppression of postprandial hyperglycemia in a prediabetic, the treatment of non-insulin-dependent diabetes mellitus, the treatment of autoimmune diseases such as arthritis and articular rheumatism, the treatment of intestinal mucosa diseases, growth

acceleration, the inhibition of rejection of a  
transplantate, the treatment of corpulence, the  
treatment of eating disorder, the treatment of HIV  
infection, the suppression of cancer metastasis, the  
5 treatment of prostatomegaly, the treatment of  
periodontitis, and the treatment of osteoporosis.